CHEMOTHERAPY OF MALARIA

Search No 893

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CHEMOTHERAPY of MALARIA

Part I

Introduction and Biological Background

by

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Chemotherapy of Malaria - Part I

Introduction

This search on the chemotherapy of Malaria was prepared as a background for the research program on anti-malarials being carried on at the Stamford Research Laboratories of the American Cyanamid Company

In view of the present emergency, and of the need for as wide an attack as possible on the problem, Lederle Laboratories, Inc , a unit of the American Cyanamid Company has prepared a limited edition which is available to research workers and investigators in this field

I Plan of Approach

The general topic malaria is so vast in its scope that complete coverage would be impossible within the time which could reasonably be allotted to this search

However, it appears self-evident that the review must, of necessity provide some background of biological and statistical information against which the chemotherapeutic aspects may be viewed The mere statement that a drug shows activity against the schizonts of Plasmodium Falciparum, for example cannot mean much unless one knows what a schizont is and where Plasmodium Falciparum fits into the picture

Accordingly Part I of this review is devoted to providing the background in sufficient detail, but without claiming completeness in any particular aspect, to enable the reader to more readily appreciate the significance of the ensuing data and also to permit a more intelligent appraisal of the current literature as it appears

The chemotherapeutic sections of the search are units within themselves In view of the fact that, at the present time interest is centered upon the sulfonamide drugs, it has been deemed expedient to put this phase of the anti-malarial study first, that is in Part II

Subsequent sections cover other branches of therapeutic agents as for example, the Use of Amidines as Anti-malarials part III, Quinoline Compounds as Anti-malarials, part IV Acridine Compounds as Anti-malarials, part V and so forth

In preparing this review on the Chemotherapy of Malaria the following reference sources have been consulted -

Abstracts of the American Chemical Society, Chemisches Zentrallblatt, Index Medicus, Tropical Diseases Bulletin Friedlander's Fortschritte der Theerfarben-fabrikation and such reviews as are available in Fischl and Schlossberger-Handbook of Chemotherapy(1933), Von Oettingen-Therapeutic Agents of the Quinoline Group(1933), Cecil-Textbook of Medicine, 4th Edition(1939), and Dyson Recent Advances in Chemotherapy (1939)

The search has been carried as far as possible through

II Malaria Defined (11)(43)(59)(16)(48)(44)

Malaria may be defined as a group of infectious fevers, caused by penetration and destruction of the red blood cells by a protozoan parasite, and characterized by paroxysms of intermittent fever which may occur daily (quotidian fever), every other day (tertian fever) or every fourth day (quartan fever), or the fever may be continuous, with marked remissions

Less commonly a pernicious rapidly fatal form, or a chronic type with anemia and enlarged spleen is observed

Although the disease has been recognized since the time of Hippocrates (450 B C) in Europe, and probably earlier in China and India it was not until 1753 that Torti attempted to classify the malarial fevers, and first used the name malaria

The word malaria is derived from the Italian words mal-bad and aria-air in line with the belief held by Torti amongst others that malaria was caused by the "bad air" or miasm which rose from the ground particularly in low swampy places.

In 1827 Macculloch introduced the word into the medical literature to define the syndrome which prior to that time was widely known under a variety of descriptive names such as "marsh miasm", "marsh fever", "paludal poison", "ague", "intermittent fever", "remittent fever", "hill fever", "fever of the country", "fever and ague", "periodic fever", "paludism", "coastal fever", "tropical fever", "endemic fever", "acclimatization fever"

Of all these names, in addition to malaria itself, only the French paludisme and its Spanish equivalent paludismo are now in scientific use.

III Clinical Manifestations of Malaria (11)(16)(26)(15)(48)(44)

(a) Intermittent Fever

Infection by malaria is usually followed by a period of incubation which may vary in length from 10 to 15 days

At the close of this period the patient may be seized quite suddenly by a paroxysm of ague which may or may not be preceded by a period of general malaise (the so-called prodromal period) characterized by headaches yawning, nausea, vomiting and uneasiness The ague starts with chills in the lower back and gradually increases in scope and intensity until the muscles of the patient's entire body tremble, his teeth chatter and a coldness extends over the skin Often the chill is preceded by a fever which may not be externally apparent but which is detectable when the temperature is taken

At the height of the rigor the features become pinched and blue, the skin acquires a shrunken appearance and the extremities turn dead white, the nails turning blue This phenomenon is generally considered to be due to a spasmodic constriction of the surface capillaries

Internal changes also become apparent The spleen swells and becomes readily palpated, the heart becomes gorged with blood and the kidneys congested The body temperature at this stage may be from 103°-106°F despite the external appearance

The first stage of the typical malaria paroxysm may last for two hours following which the second stage ensues It is characteristic of the malaria rigors that they usually occur between midday and midnight, a fact which serves to distinguish malaria from other fevers (2)

The second period the period of dry heat, is manifested by a change in the symptoms The body becomes flushed and dry, the surface arteries throb visibly and the patient is actively delirious Internally the spleen continues to enlarge, and the body temperature remains high but the kidney congestion decreases

After three or four hours of the second stage of the paroxysm the fever breaks, a vigorous outpouring of perspiration occurs and the patient often falls asleep Up to this point the paroxysm covers a period of from 6 to 12 hours

When the patient awakes, his condition is practically normal and remains so for a definite period of time dependent upon the type of malaria involved, following which another rigor sets in The period of freedom from symptoms is called the "intermission" of the fever

If the next paroxysm occurs at the same time the following day the patient has quotidian malaria, if forty-eight hours later, tertian malaria and if seventy-two hours later quartan malaria.

(b) Remittent Fever.

Remittent fever is characterized by the fact that the first paroxysm does not cease within twenty-four hours In such cases the cold stage of the paroxysm is shortened while the hot stage tends to be prolonged There is usually some abatement of the fever with or without sweating but no real intermission during which the symptoms are absent

Such a fever begins with chills but lacks the tremors seen in the intermittent type The hot stage then follows with biliousness, jaundice and tenderness over the liver After a period the fever abates, painful symptoms are less and the body temperature falls somewhat This remission lasts throughout the morning and about noon the symptoms increase in severity until the following morning when another remission occurs.

In such cases, as the patient recovers, the fever remissions usually assume the character of intermissions in which periods of complete apyrexia obtain.

Remittent fevers are most commonly caused by the estivo-autumnal parasite and occur usually in temperate or sub-tropical climates in the late summer and autumn.

(c) Pernicious Malaria

Pernicious malaria is the title given to the disease when the parasite localizes in certain organs Here the congestion causes severe paroxysms due to the abnormally large number of organisms present

Pernicious malaria appears usually as one of three general types, namely,

1 Cerebral - characterized by severe disturbances of the central nervous system with delirium and coma The comas last for 1 1/2 to 24 hours with high fevers but no chill This form of the disease appears to be due to blocking of the cerebral capillaries by the parasite

2 Algid(Asthenic, Cardiac or Adynamic) - characterized by extreme gastro-intestinal disturbances, vomiting and diarrhoea with sub-normal temperature This form appears to be due to blocking of the capillaries of the interstitial mucosa by parasites

3 Hemorrhagic - characterized by hemoglobinurea where hemolysis of the blood takes place due to enormous number of parasites destroyed

(d) Chronic Malaria

As the name implies chronic malaria is a sub-acute form of the disease. It is characterized by cachexia accompanied by dyspnoea upon exertion, edemas, and hemorrhages, particularly retinal hemorrhages, and enlarged spleen.

(e) Malarial Relapses (Recidives)

Although the exact cause for relapses in malaria is not known it is presumed that they are due to the fact that some of the parasites remain latent for an indefinite period of time until some circumstance causes re-establishment of the disease in the acute stage Relapses have been known to occur as long as three years after the original infection.

(f) Cause of Death in Malaria

In general, direct attacks of intermittent fever account for but a relatively small proportion of the total deaths Remittent fever is much more likely to terminate fatally Probably fifty per cent of the fatal cases of malaria are of the cerebral type.

Another of the chief sources of death from malaria is the general debilitation due to chronic malaria This last form leads to gradual breakdown of the body mechanism with death ensuing in a high percentage of cases

Of the intermittent fevers the most likely to result in death is that caused by the falciparum parasite This parasite owes its deadliness to its high rate of reproduction and to the fact that it produces a sticky substance which causes the blood cells to stick together with consequent obstruction in vital parts

Knisely et al (37) have recently established that malaria may kill by turning the fluid blood into a thick sludge which plugs up the small arteries and veins By so doing the heart becomes overtaxed trying to pump blood against the blockade of malarial sludge and may fail entirely, with resultant death

Etiology of Malaria

(a) Causative Agents of Malaria (16)(48)(59)(25)

Prior to the year 1880 the dominant theory elaborated to explain the causation of malaria was that it was due to the pernicious influence of a miasm which arose from the ground during the night and particularly in low swampy localities Hence, the idea that night air was dangerous

In 1880, however, Laveran, who was making a microscopic study of the blood of a malaria patient, observed the presence of a foreign organism therein which he proceeded to identify as a plasmodium This plasmodium was later demonstrated to be a form of the malarial parasite.

Following this observation the study of this organism was taken up in Italy where, in 1885, Marcheafava and Celli published the first accurate description of the parasite The Italian school of bacteriologists then proceeded to elaborate the life cycle of the plasmodium in man and in so doing showed that the malarias have definite etiological as well as clinical destinctions

The next big step in the study of the malarial parasite was made by Sir Patrick Manson in 1894 when he suggested that, in order to explain the mode of transmission of the disease it was necessary to conclude the existence of an intermediate host outside the human body. This intermediate host, he deduced, should be, by the nature of things, a sucking insect.

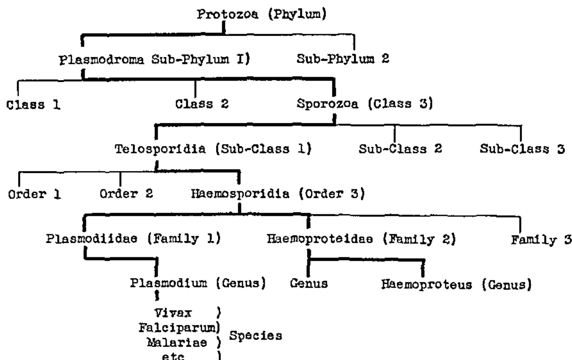
Within the next three years the truth of Manson's suggestion was established by Ross who, following the suggestion of Dr. W H. Welch, observed pigmented cells in the intestines of certain mosquitoes These pigmented cells he then proceeded to demonstrate, by experiment, to be a form of the malarial parasite Ross, furthermore, succeeded in proving that the specific intermediate host for human malaria was the Anopheles mosquito and he elaborated the life cycle of the plasmodium in this vector

The study of the malarial parasite still goes on Much that relates to the subject still remains obscure However, since such refinements do not have particular significance in this particular study no attempt will be made to go into them.

(b) The Malarial Parasite (15)(16)(11)(25)(34)(2)

The malarial parasites are classified by protozoologists (40) as indicated in Table I below. In order to simplify consideration of the table, only the pertinent data have been included In addition to the malarial parasites, however, the classification of Haemoproteus has been added so that the relationship between this organism and the plasmodia may be seen. This is done since haemoproteus infections have been used to test anti-malarials, and the question as to the validity of such test results as a criterion of anti-malarial activity depends in part, upon the closeness of the relationship between the two types of organism From the table it is apparent that the relationship is close and consequently the chances that a carry over exists are reasonably plausible

Table I



A great many plasmodia have been isolated and studied and a large number of these are of interest in the chemotherapy of malaria

The most important plasmodia from our point of view are the following which are classified according to the host in which they are most commonly found

Man	Monkeys and Apes	Birds
Pl Vivax	Pl Knowlesi	Pl Cathemerium
Pl Falciparum(syn	Pl Inui	Pl Capistrani
Pl Immaculatum)	Pl Cynomolgi	Pl Praecox
Pl Malariae	Pl Brasilianum	Pl Danilewskyi
Pl Ovale	Pl Kochi	Pl Relictum
Pl Pleurodyniae	Pl Pitheci	Pl Lophurae
Pl Tenue	Pl Reichenovi	

Also of interest is the fact that many chemotherapeutic tests against malaria have been carried out on birds infected with Haemoproteus (31)

The most important parasites from the human point of view are, of course, Pl vivax, Pl falciparum and Pl malariae which are the cause of most human malaria Fig 1 of Boyd (8) shows the distribution of these three parasites throughout the world

The plasmodia are closely related morphologically although each gives rise to a characteristic syndrome

The expectation which might be assumed (in view of the close relationship) that chemotherapeutic agents which are active against any one plasmodium or against Haemoproteus would also be active against any other has not, however, checked expectation and one of the greatest problems facing the pharmacologist today is to obtain means of translating test results in apes or birds in terms of action against human malaria

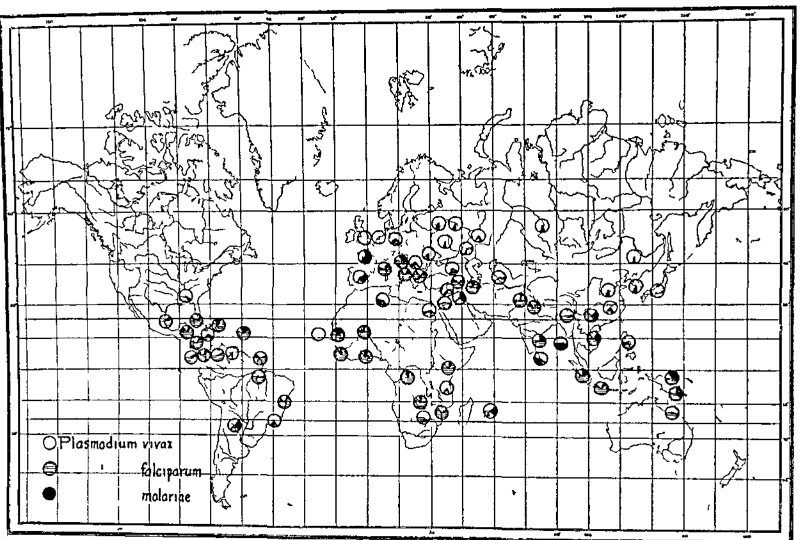


Figure 1

from Introduction to Malariology M F Boyd M D

(c) Relationship Between Clinical Symptoms and Species of Parasite

In this connection consideration will be given only to the three malarial parasites which are the common causes of human malaria namely Plasmodium Vivax, Plasmodium Falciparum and Plasmodium Malariae

Plasmodium Vivax is the causative parasite in Benign Tertian malaria This disease derives its name from the fact that it is rarely fatal and from the periodicity of the rigors No other fever shows the regular 48 hour rise in temperature of an intermittent nature This parasite is found all over the world

Plasmodium Falciparum also known as Plasmodium Immaculatum is the causative parasite in Malignant Tertian Sub-Tertian Aestivo-Autumnal or Pernicious Malaria The parasite has a 24 to 48 hour cycle and is the most deadly of all the plasmodia attacking man. The high mortality due to this parasite may be ascribed to (A) the rapidity of its multiplication and to the resultant rapid destruction of blood cells (B) the fact that it invariably localizes in an internal organ and (C) the peculiarity of this organism whereby it produces sticky substances which cause the cells to stick together causing obstruction of vital parts Plasmodium Falciparum is prevalent in the tropics, in the Mediterranean and in sub-tropical American regions

Plasmodium Malariae is the causative agent in quartan malaria Quartan malaria is not very common This form of fever is manifested by a 72 hour period between rigors

The differential relationship between these three parasites may be seen from Table II

Table II

Differential Diagnosis of Malarial Parasites of Man

Topic	Pl Vivax	Pl Malariae	Pl Falciparum
Type of Fever	Benign Tertian	Quartan	Malig-Tertian, Sub-Tertian Aestivo-Autumnal
Length of Cycle	48 hours	72 hours	24-48 hours
Stages in Peripheral Blood	All	All	Trophozoites and Gametocytes only
Abundance of Parasites	Intermediate No	Lowest No	Highest No
Red Blood Cells	Enlarged-Decolorized	Normal-Unaffected	Misshapen-Discolored
Trophozoites	1/3 Diam Red Blood Corpuscles	1/3 Diam Red Blood Corpuscles	1/6 Diam Red Blood Corpuscles

(continued)

(continuation)

Topic	Pl Vivax	Pl Malariae	Pl Falciparu
Schizonts	Amoeboid-Large	Elongate-Oval Medium	Round-Small
Merozoites per Schizont	15+	8-10	8-10
Gametocytes	Rounded	Rounded	Crescentic

(d) Life Cycle of Malarial Parasite (2)(8)(11)(15)(16)(25)(32)(43)(48)

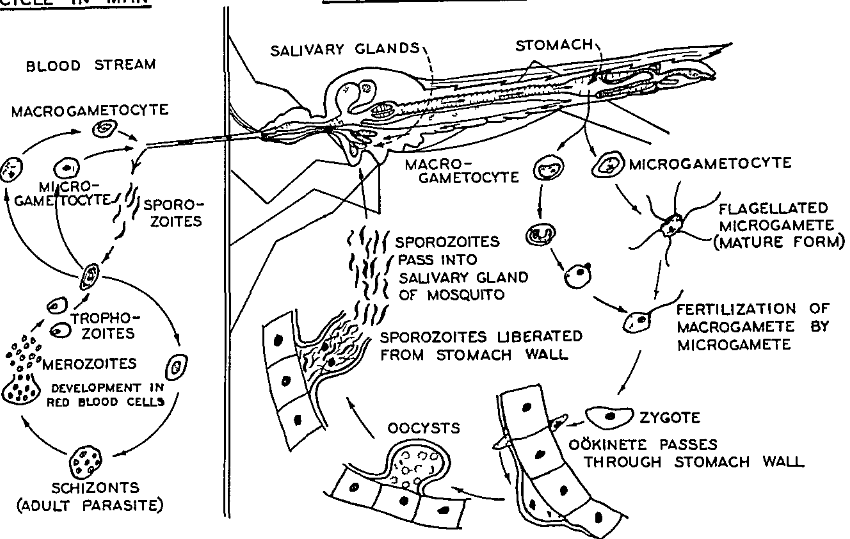
The life cycle of the malarial parasite or plasmodium involves three separate and distinct phases namely, schizogony, gametogeny and sporogeny Of these the first stage takes place entirely in the human host, the second serves to link the human and extra corporeal host, i e the mosquito, and the third phase occurs entirely within the mosquito This relationship may be seen at a glance from the diagram (Fig 2) showing the digenetic life cycle of the Malarial Parasite (66)

1 Life Cycle of Plasmodia in Man

When a malaria infected mosquito bites a victim, saliva is injected into the blood stream This saliva is teaming with slender spindle shaped organisms having central nuclei and a length of about 10μ These organisms which are called sporozoites become distributed throughout the blood and proceed to attack the erythrocytes Once attached to the red blood cell the sporozoite changes its shape to a ring form about 3μ in diameter having a brightly staining eccentrically placed nucleus The trophozoite grows at the expense of the cell substance, liberating waste products which appear as pigment in the cell, until development has reached the stage of maturation when it becomes a schizont or asexual form of the parasite The schizonts then undergo a process of asexual reproduction (schizogony) with the formation of a number of merozoites or young forms. The number of merozoites produced depends upon the parasite involved, varying from 8 - 32 per schizont The cell now ruptures and discharges the merozoites into the blood stream The time taken for this to occur varies considerably with the species of parasite being 24 - 48 hours in estivo-autumnal malaria, 48 hours in tertian malaria and 72 hours in quartan malaria Many of the merozoites are destroyed by phagocytosis, but the remainder attack further cells and continue the destructive cycle However, another, little understood phenomenon, may also occur Some of the schizonts or merozoites undergo a metamorphosis and become sexual forms of the parasite, i e. the micro (male) and macro (female) gametocytes These gametocytes apparently have no function in the human host but await transmission to the mosquito where they continue their active existence.

2. Life Cycle of Plasmodia in Mosquito

When a susceptible mosquito bites an infected human, blood containing both merozoites and gametocytes enters the stomach The asexual forms of the parasite soon die but the sexual forms, sometimes called crescents undergo maturation (gametogeny) and become micro and macrogamete



THE LIFE CYCLE OF THE MALARIAL PARASITE

body fluids They ultimately penetrate the macrogametes and the sexual cycle begins (*sporogony*) The result of the fusion is a zygote which elongates and turns into a motile oökinete The oökinete penetrates the stomach wall and encysts on the exterior thereof forming an oöcyst The organism undergoes growth in the oöcyst becoming a sporont which then subdivides into sporoblasts which cause the cyst to rupture by which means they escape into the body cavity as sporozoites The sporozoites wander finally into the salivary glands of the mosquito and await transfer to a suitable host in order to continue the cycle.

(e) Relationship Between Clinical Symptoms and Malarial Life Cycle

There are three stages of the pyrexial attacks which according to Nocht and Mayer (48) may be directly correlated with three distinct phases in the development of the parasite, as seen in Table III

Table III

Stage of Fever	Stage in Parasite Development
Shivering Stage	Schizonts and young forms predominate
Fever	Parasites least numerous, schizonts not found, young forms predominate
Sweating Stage	Development of Parasites well advanced, due to be completed in the next afebrile period

It is now established quite definitely that the onset of the typical paroxysm of malarial fever corresponds to that phase in the plasmodial life cycle wherein the cells rupture and the merozoites or young forms are suddenly liberated into the blood plasma

The reason for the particular phenomenon brought on by this occurrence is not known However, it seems clear that it is due to the liberation of some toxin into the blood stream along with the merozoites

Goodman and Gilman (21) state that in a single febrile spasm as much as 1/5 of the circulating red cells may be destroyed and assuming that toxin is liberated from each cell it is easy to understand the intensity of the ague in malarial fever.

It was once thought that the chills might be bound up with the hypoglucemia which accompanies attacks of malarial fever but Otero (49) and Lenzi (42) disproved this and established that the change in blood sugar was due to damage to the liver parenchyma

Zweimer, Sims and Coggeshall (67) have recently found that there is always a sharp rise in plasma potassium whenever sporulation occurs This rise may be as much as 50% and is always highest at the time of chill, falling before the drop in temperature occurs On this basis the authors postulate that this potassium release from the red cells and its inadequate regulation by the body may be a toxic factor At the very least it is definitely associated with the malaria chill

Whatever the direct cause of the chill it must apparently overcome a threshold value before it makes itself manifest since it has been found that there must be at least 50 parasites per cubic centimeter of blood before a rigor can occur (2)

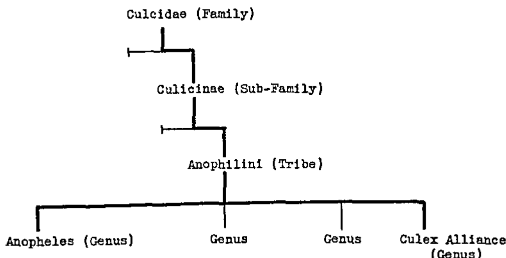
(f) Malarial Vectors (Transmission of Malaria)

1 The Anopheles Mosquito

As indicated earlier, the malarial parasite spends part of its life cycle in the gut of the mosquito In 1898 it was definitely established that the particular vector for malaria is the Anopheles mosquito

Entomologically, according to Anderson (2), the Anopheles mosquito is placed as follows

Table IV



Of the 3000 odd species of mosquito which according to Shute (56) infest the world only a comparatively few are commonly known to be transmitters of malaria In different sections of the world the particular species which are the prime vectors differs

Dorland (15) lists the following species of Anophelines as the best known carriers of malaria with their commonest habitat

Anopheline Species	Habitat
Albimanus	Tropical America
Albipes	Tropical America
Argyrotarsus	Tropical America
Bancrofti	Australia
Costalis	Africa
Crucians	Southern United States
Culicifacies	India
Funesta	Africa India(64)
Listoni	China, India, Japan
Ludlowi	East Indies and Philippines
Maculipennis	Europe
Neomaculopalpus	Panama Canal Zone
Punctimacula	Panama Canal Zone
Punctipennis	Temperate America
Quadrimaculatus	North America

(continued)

(continuation)

Anopheline Species	Habitat
Sinensis	China, India and Japan
Stevensi	India
Umbrosus	Malaya
Willmori	Malaya
Cruzi	Brazil
Furcatus	Europe
Eiseni	Central America

This list is incomplete, however, the situation in each section of the world demanding a more complete survey in order to get a clear picture of the vectors which are active

For example, in Malaya, five out of the forty-one species of Anophelines found there have been indicted as active carriers of malaria (4) The preferred habitats of these mosquitoes give some idea of the difficulty of finding a single means of working their destruction A maculatus inhabits sunlit streams, A umbrosus and A novumbrosus prefer swamp waters, A sundaicus is addicted to brackish water and A barbirostris breeds in pools

Of particular interest to us, however, is the situation which exists with respect to the Americas and particularly the United States.

Anderson (2) gives three species of anophelines as the commonest vectors of malaria in the United States, namely, A quadrimaculatus, A punctipennis and A crucians and, of these, places the first as the most important Hinman (29) has found quadrimaculatus to be a prolific breeder in the reservoirs of Alabama, particularly when flotsam is allowed to collect on the surfaces Boyd (8) published a map of the United States, reproduced here as Fig 3, which shows the distribution of five species of anopheline throughout the country.

In the Canal Zone, Simmons (57) lists 15 or more species of anophelines, of which the following have been found to be infected with malaria A albimanus, A albitarsis, A tarsimaculatus A bachmanni, A argyritarsis, A pseudopunctipennis, A eiseni, A apicimacula A neo-maculipalpus and A punctipennis Of these the really important vectors are given as albimanus, punctipennis and tarsimaculatus

In South America in addition to the anophelines listed by Anderson (2), fear was expressed by Fosdick (17) a few years ago that the accidental introduction of A gambiae into Natal, Brazil in 1930 was a menace, which could not be ignored, since, this mosquito was spreading rapidly at the rate of about 40 miles per year and spreading malaria with it Recently, however, news has appeared indicating that success in stopping the advance of this pest upward towards the United States has been achieved

The study of the anopheline mosquito occupies the attention of many research men throughout the world since, one possible method of eliminating malaria from the world would be to eliminate all the carrier mosquitoes. Great advances are being made along these lines by oiling breeding places, eliminating water collection by adequate drainage and by the use of larvicides.

This phase of malariology may have features of interest to the insecticide groups but must be skipped in favor of those aspects more of interest from the chemotherapeutic point of view

2 *The Culex Mosquito*

The culex mosquito is not a carrier of human malaria.

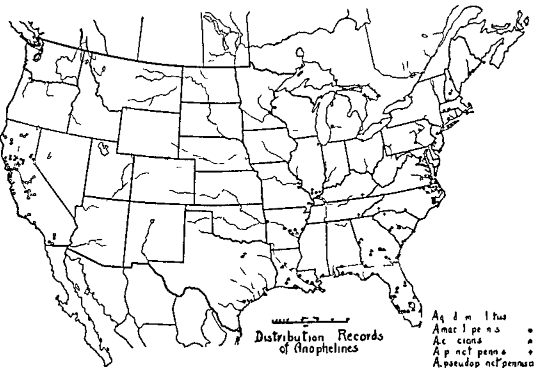


Figure 3

from Introduction to Malariology M F Boyd M D

However, it is used extensively to transmit experimental malaria in birds

3 Transmission of Malaria via Drug Addicts

Biggam (6) in 1929 was the first to record an epidemic of malaria amongst drug addicts in Cairo Three years later Geiger (19) reported on a case of malaria in a drug addict in the United States and in 1934 Helpern (24) told of an epidemic of malaria amongst drug addicts

Since then many authors have called attention to the dangers attending this situation Boyd and Schlackman (9) point out that the fatality from malaria amongst drug addicts is about twenty times as high as the ordinary death rate, the highest mortality being from the aestivo-autumnal parasite.

Such protozoal diseases are transmitted usually by the common use of a single hypodermic syringe by a number of drug addicts, one of whom happens to have malaria (3) (10) Clinically and pathologically the disease manifests all the characteristics of malignant malaria as seen in the tropics including the cerebral and intestinal manifestations It is pointed out that anopheles quadrimaculatus breeds in New York City and its immediate environs and could easily become infected causing a possible epidemic.

Gowan (22) and Most and Jolliffe (47) point out that Falciparum malaria is endemic in New York City amongst drug addicts The same condition is also found in other large cities such as Chicago Both the benign (Pl vivax) and the malignant tertian (Pl falciparum) strains of parasite are found In New York at least 200 cases of malignant malaria have been reported since 1934 and in Chicago and New York, respectively from 1937-1939 forty-one and forty-six per cent of the total cases were drug addicts (46)

Gowan (22) also reports that three outbreaks, totalling 18 cases, have been reported in which the disease may have been transmitted by Anopheles mosquitoes from inoculated paretics, as a result of laxity in the isolation and terminal release of those receiving the malaria therapy

V Epidemiology - Incidence and Distribution of Malaria (11)(59)(66)(25)(16)

The origin of malaria is buried in the unwritten files of history However it is known that Hippocrates (11) around 450 B C gave a description of quotidian tertian and quartan types of intermittent malarial fever which is recognizable today Likewise, Plautius in 184 B C described malaria and according to Boyd (8) Empedocles of Agrigento as far back as the 5th century B C recognized the injurious effects of stagnant water and is credited with having cleared the city of Silenus in Sicily from endemic fever by changing the drainage From these facts it is apparent that the coast of the Mediterranean was full of malaria

Malaria was described by Morton in 1697 as being widespread throughout England and Wales and in 1726 intermittent fevers were rife in England and Scotland

Holland was highly malarious at the commencement of the 19th century as were also Germany and France

In the United States conditions were also bad in the 17th century. Hirsch (30) states that in New England a series of malaria epidemics swept Massachusetts in 1647, 1650 and 1668

One hundred years ago Minnesota and Michigan and the general region around the Great Lakes were full of malaria Seventy-five years ago malaria was one of the important diseases in the large centers of New England, Maryland, Ohio and Southern Illinois, and shortly prior to the opening of the twentieth century the disease was prevalent in New York, Philadelphia and Baltimore

It is a peculiarity of malaria that as civilization advances the prevalence of the disease recedes Dr Frichs of the Malarial Investigation of the United States Health Service is quoted as having said in this connection "During the past 50 years the area of endemic malaria in the United States has shrunk to less than one-third of its former extent without any effort on the part of the Health Authorities to control the disease At the time of the Civil War malaria was the largest single cause of death in the Southern States, hemoglobinurea and coma being common During the World War it was a negligible factor in the health of a very much larger number of soldiers in service" (59)

Despite this fortunate circumstance however the scourge of malaria should not be minimized Even today there is probably no other disease that stands in the same class from the point of view of the bodily, economic and political losses which follow in its train

A glance at the map Fig 4 (8) will give some idea of the wide extent of the disease even today It is prevalent in Africa, Spain, Southern France Italy Greece Turkey, Russia, Palestine Iraq, Syria, Arabia, India, Ceylon, Malaysia, China Japan, Siam, New Guinea, Solomon Islands, Bismarck Archipelago, West Australia, North of South America, Chile, Peru, Columbia, Brazil, Paraguay, Bolivia, Mexico, the shores of the Caribbean, the Mexican Gulf and the Southern States of the U S A

In China, L L Williams (65) states that "malaria is responsible for more deaths than all the other infectious diseases in Yunnan Province and hundreds of thousands of young adult lives are damaged annually"

In 1932 the League of Nations sent out questionnaires to the Governments of 100 countries infected with malaria From the replies it was gathered that 17,500,000 patients were treated annually In India, only 8,000 000 to 10,000,000 of the probable 100,000,000 cases were treated

Within the British Empire malaria still heads the list of diseases and more than 3,000,000 deaths are recorded every year throughout the world

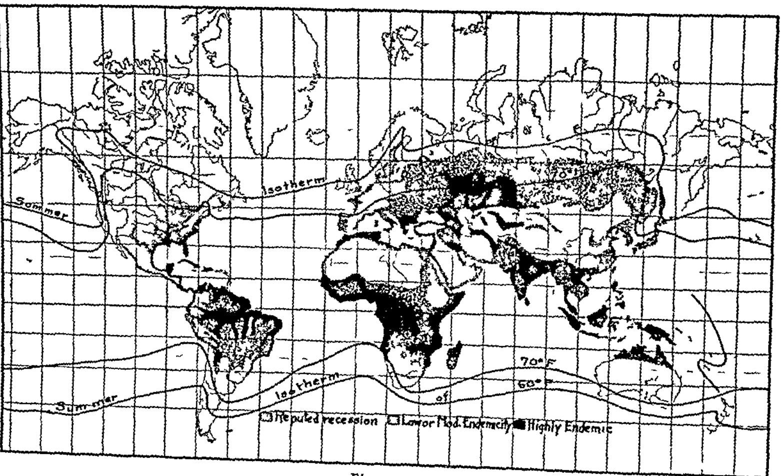


Figure 4

from "Introduction to Malariology" M F Boyd M D

A glance at the map Fig 5 (8) will show the extent of malaria within the United States As may be seen it is mostly restricted to the Southern states in the neighborhood of the Caribbean Sea

In Mississippi one county alone treated 8,236 cases annually from 1914-1918 with an average of 77 deaths per year A report for the United States (62) covering the year 1939 cites 82,655 cases of malaria during the year with a registered death rate of 1,750 or 0 013 per 1000 of population

The morbidity however, does not give a true picture of the effects of malaria More important by far is the tremendous debilitating effect of the disease with loss of time and efficiency

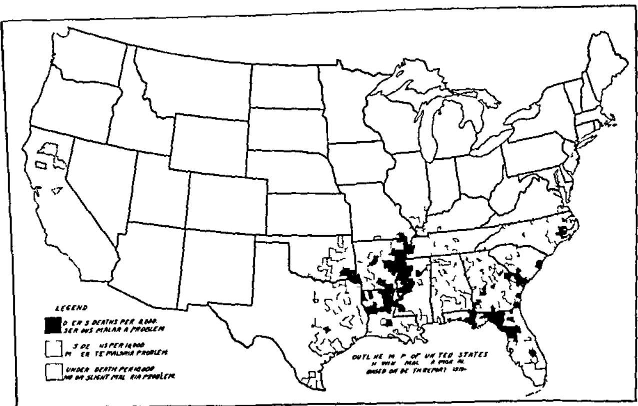


Figure 5

from Introduction to Malariology M F Boyd M D

VI Chemotherapy of Malaria

(a) Testing Drugs

All the early investigations on the use of the cinchonas against malaria, as is well known, were carried out on patients who were suffering with the disease

When the study of chemotherapeutics began to expand it became apparent that a test animal would have to be found in order to properly evaluate the synthetic compounds which were being prepared

Considerable work was done on paramoecia as test animals but it was recognized that the results obtained were not of much value

(b) The Use of Birds as Test Animals

When the I G began the chemotherapeutic studies which led to the discovery of Plasmochin, Roehl (51) introduced birds as test animals The fact that birds were susceptible to malaria had been mentioned in 1885 by Danilewsky (14) following which Laveran (41) in 1890 presented a series of papers intended to stimulate medical men to other investigators played an important part in the general study of bird malaria, namely, Et and Ed Sergent (55), Ruge (52), Wasielewski (63), Marks and Brünn The culmination of the long study of bird malaria was the paper of Ben-Harel (5) in 1923 on the nature of the malarial infection in birds and three years later Roehl published the first paper in which a technique for the use of birds in testing drugs was disclosed

After the death of Roehl his work was continued by Kikuth who studied a variety of strains of bird malaria and who finally found the haemoproteus infection of the paddy bird to be a valuable tool in the study of anti-malarial drugs (31)

The development of the use of avian malaria as a test means was not restricted to any one group Fourneau and Bovet (18) in France were carrying on studies much in the same vein as Kikuth in Germany Collier and Krause (13) introduced the use of the Java sparrow in 1929 and in 1931 Roehl's method was supplemented by using canaries infected by mosquito bite instead of by straight blood inoculation (33) Magidson et al in Russia used siskins for their tests and introduced the idea of injecting the drugs instead of feeding them, a method used also by Fourneau Kikuth and Schönhöfer (36) in 1935 discovered the value of Atebrine by test on bird malaria

1 Methods Used in Bird Tests (25)(28)

Although different investigators introduce variations into their individual test methods certain general principles are now available

Roehl, in his original procedure used canaries as his test animal His method comprised treating a number of canaries infected by inoculation with blood from a previously infected bird, leaving a few birds untreated as controls The drugs were introduced by mouth and the number of days of retardation of the time of appearance of parasites in the peripheral blood was taken as a measure of the efficacy of the drug

Since both the sexual and asexual forms of the parasite appear in the peripheral blood of the canary a positive result for any

drug would not differentiate between schizonticidal and gametocidal drugs

To overcome this difficulty the test was later augmented by tests in Java sparrows. In the Java sparrow (Orizonis Orizivor) infected by Haemoproteus, an organism very much like the malarial parasite (see Table I) only the sexual forms of the protozoan appear in the blood. Accordingly, by carrying out tests on such birds in the same way as on canaries (the presumption being that drugs effective in Haemoproteus infections will be effective in malaria) positive results would indicate a gametocidal drug.

If the drug is active in canaries, but not in sparrows it must be effective only against schizonts A drug which attacked both schizonts and gametocytes would appear in these tests as a gametocidal drug

The question which always arises in any animal test of drugs intended for human use is whether there really is any carry over, that is, whether the tests constitute valid criteria for activity in humans.

Concerning the tests on birds Wasielewski (63) showed, as early as 1905, that quinine which was known to be useful against human malaria was also active against bird malaria (praecox) This work was also extended and found to hold for other alkaloids related to quinine by Kopenaris (39), Et and Ed Sergent (55), Morgenroth (45) and Giemsa (20) In addition the relationship was checked by Roehl (51) on plasmochin and Kikuth (36) on Atebrine

Hegner, Shaw and Manwell (23) at Johns Hopkins University have been active in the field of avian malaria Boyd (7) repeated the work on quinine and quinine derivatives in 1926 and checked the workers listed above.

This work seems to corroborate the belief that drugs which are active against bird malaria will also be active against human malaria However, this is not entirely borne out by the results of Coggeshall of the Rockefeller Institute who has tested some of the sulfonamide drugs on birds without positive results but has found that certain of the negative drugs are active against human malaria

(c) Use of Paramoecia to Test Drugs

Concerning the Paramoecia - Hegner, Shaw and Manwell (23) point out that in order to obtain some idea of the toxicity of drugs to protozoa they test them against Paramoecium caudatum as a routine step. They recognize that the degree of toxicity to a highly specialized infusorian such as Paramoecium is a poor index but since the plasmodia cannot be easily cultured this organism is used instead They point out that quinine and the related alkaloids are toxic to Paramoecia in proportion to their effectiveness in the treatment of malaria and accordingly consider that the method may have some value.

(d) The Use of Monkeys as Test Animals (8)

The systematic use of monkeys for experimental work dates from the year 1932 In that year Napier and Campbell and Knowles and Das Gupta (38) described the malarial parasite which infects monkeys (Macacus Irus) in India, this parasite was called Pl Knowlesi by Sinton and Mulligan (58) in honor of its discoverer This organism is also highly virulent for Macacus rhesus

The application of these animals to the study of malaria and the study of the relationship between human and ape malaria has pro-

gressed with great rapidity Soon after 1932 Van Rooyen and Pile and Nicol used Pl Knowlesi for infecting paralytics, and in 1934 Taliaferro and Cannon (60) successfully transmitted malignant tertian malaria to screech apes

Other workers also succeeded in transmitting ape malaria to humans thus establishing that the higher apes are infected with malarial parasites which are morphologically similar to the human parasite.

This information has been put to use in the testing of drugs in recent years as may be seen from the schedule of tests of sulfonamide drugs against malaria

(e) In Vitro Studies

Recent attempts are being made to develop a method of testing anti-malarial drugs against parasites grown in vitro Great difficulty is experienced in trying to obtain good and prolonged propagation of the protozoa

Hewitt (27) was able to obtain growth of Pl Cathemerium by introducing blood from a bird heavily infected with the parasite into a medium consisting of inspisated whole egg slants covered with 10 cc of 0 9% saline containing 0 5 per cent dextrose and serum from a bird or rabbit The culture was incubated at 37°C

Coggeshall has been investigating the use of in vitro studies to determine the effect of the sulfonamide drugs The method involves the determination of the inhibition of oxygen uptake of protozoa by drugs added to the protozoa in a Warburg apparatus.

(f) Status of Malarial Chemotherapy

Up to the present time many classes of compounds have been tested as antimalarials However, only a relatively small number of drugs are of active clinical importance, namely, Quinine, Atebrin and Plasmochin, with possibly neoarsphenamine as a runner up

Of these drugs quinine is effective against schizonts and young forms of the parasite It is inactive against sporozoites and ineffective against gametes

Atebrin (2-methoxy-6-chloro-9-α-diethylamino-δ-pentylamino acridine) has activity of much the same order as quinine but is even less effective against gametes

Plasmochin (6-methoxy-8-diethylamino isopentylamino quinoline) has activity against the gametes or sexual forms of tertian, and sub-tertian malaria It does not affect the sporozoites and is ineffective against the trophozoites or young forms

Neoarsphenamine, which is occasionally used with the above drugs has a partial effect against schizonts

(g) Sources of Drug Supply

Quinine - Practically the whole world's supply of quinine is obtained from Java from which source it is distributed by the Kina Bureau (its selling agent) (1) Recent world developments have led Agricultural authorities to give serious consideration to the utilization of sources of possible supply which are not at present exploited For example in 1940 advices were received by the Department of Commerce from the American Consulate in Columbo, that it was contemplated to erect a quinine factory in Ceylon (50). India

also has some quinine plantations which may at some future date take over a greater part of the burden of supply

Atebrin and Plasmochin - Both of these drugs are manufactured under German owned patents In the United States the sole manufacturer is the Winthrop Chemical Company

(h) Need for Anti-Malarial Research

In May of 1940 at a meeting of malariologists at Atlanta, Ga , at the initiation of the Surgeon General of the United States Public Health Service the problem of the chemotherapy of malaria was considered It was pointed out that in view of the urgent world conditions together with the fact that the activity of available drugs is limited one of the most pressing problems lay in the field of chemotherapy (1)

The need for malaria research was also voiced by the Division of Chemistry and Chemical Technology of the National Research Council To further the development of chemotherapeutic research in the United States the National Research Council appointed a committee which has the assignment to study the status of anti-malarial research The members of this Committee are as follows - L T Coggeshall, L H Crotcher, L F Small, T H Sollmann and M T Bogert.

Whether the economic and political disturbances which the world is undergoing will put the United States in jeopardy with respect to the supply of anti-malarials cannot be predicted

Regardless of these facts, from the medical point of view alone there is need for improvements

It has been pointed out (1) that it would be extremely desirable to have available a drug which would destroy sporozoites, either at the time of infection or during their stay in the fixed tissue cells Such a drug would serve as a prophylactic or would prevent relapses from an infection which has been temporarily suppressed by quinine or atebrin

Under any circumstances better drugs than those now used must be made and at a price which would make them available to the many millions who suffer from the disease but who cannot afford the present cost of treatment

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CHEMOTHERAPY of MALARIA

Part II

Sulfonamido Compounds and Sulfones as Antimalarials

by

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June 1941

Table of Contents

Sulfonamido Compounds and Sulfones as Antimalarials - Part II

Introduction

Although sulfonamido substituted acridines were patented, as agents suitable for combating blood parasites in 1935 (34) the first reported test of a sulfonamido compound against malaria appeared in 1937 (19) Since that time considerable investigation has taken place covering a number of the better known sulfonamide compounds as well as specifically designed derivatives thereof To date, although the results obtained are, generally speaking, quite promising, no compound in this series has been found which could in any degree, take the place of the anti-malarials already on the market. A difficulty which has appeared in connection with the testing of sulfonamide compounds is that certain compounds which give negative results in the avian studies have shown much more activity when tried in human malaria Coggeshall (unpublished) tested the product "Promin" against Pl Lophurae in chicks with negative results only to find that the drug is effective in reducing the fevers of paretics infected with induced (benign tertian) malaria This observation has led Coggeshall to the decision to try drugs such as sulfadiazine and the like against human malaria despite the fact that they show no activity against bird malaria or in vitro

I. Plan of the Review

In the discussion of the results of tests reported in the literature it has been deemed best to cover each of the better known and commercially available sulfonamide drugs such as sulfanilamide, sulfapyridine, etc individually Substituted sulfanilamides, acridine sulfonamides, etc are covered as classes. The reason for not attempting to make the analysis more fundamental is obviously that the results are too few and too indefinite to correlate.

Following the review a table (Table I) has been included in which the data are summarized In the table are given the name of the compound tested, its formula, the name of the organism against which the tests were made, the host, the results of the tests in symbol form and the references relating to the findings given

Also included in this section is a table of trade names of the sulfonamide compounds This table is essentially the same as that prepared by Northey (39) with such additions as have been picked up in the course of this search.

In reviewing the literature on the sulfonamide drugs in almost any connection it is apparent that a knowledge of the trade names given to the compounds in various countries is essential. Many authors refer to the drugs tested only in terms of the trade name and give no indication of formula or chemical name. This procedure coupled with a lack of knowledge of the compounds to which the trade name refers can cause considerable confusion, leading to misinterpretation of a worker's paper For example the following editor's note appearing in one of the references cited (19) is indicative of such a situation "Rubiazole is the French name of one of the sulfonamide preparations, better known under the trade names of Prontosil and Prontylin" A glance at Table II will show that here the editor confuses three different compounds

The review of sulfonamido compounds and sulfones ends with a bibliography in which the references are arranged in numerical order.

II Discussion

(a) Sulfanilamide in Malaria

1 Sulfanilamide in Human Malaria

Against Pl Vivax in naturally occurring benign tertian malaria Hall (27), Niven (37)(38), Loennecken (32) and Read and Pino (43) report negative results Niven treated 80 cases of malaria with 3 grams of sulfanilamide twice daily for seven days without any substantial improvement and Hall used 40 grain doses of sulfanilamide in conjunction with prontosil solution every four hours on four cases but reported negative results

Doubtful results in the use of sulfanilamide against tertian malaria were reported by Faget Palmer and Sherwood (24) who obtained abortion of symptoms in only one out of several cases treated, Sorley and Currie (48) who treated 5 cases with 10 grains of the drug three times daily and reported apparent benefit but later relapses and Durand and Villain (23) who obtained one partial success out of 5 cases treated with 4-8 tables of sulfanilamide daily

The only reports of positive results were published by Ingalls and Gelperin (30) and Yamamoto (52) Both of these were working with induced vivax malaria which may explain the results somewhat since the disease thus acquired is probably less stubborn than the natural form Yamamoto obtained complete cures in 14 cases with only two cases resistant to treatment Ingalls and Gelperin treated three patients with 20 grains of the drug orally every four hours until 100 grains had been taken after which the dosage was reduced to 15 grains three times daily Under this treatment the parasites disappeared from the peripheral blood and decided improvement was obtained

Three reports are available on the use of sulfanilamide against falciparum malaria Faget, Palmer and Sherwood (24) report complete failure of the drug to bring about any beneficial result while Niven (37)(38) indicates indefinite results were obtained on patients given 1-1/2 grams of the drug twice daily for seven days.

Against Quartan malaria (Pl Malariae) Niven (37)(38) also reports indeterminate results from the use of 3 grams of sulfanilamide daily, given in two doses for seven days

Coggeshall (16) gives a report that Pl Knowlesi infections in humans are quickly eradicated by the use of sulfanilamide

2 Sulfanilamide in Simian Malaria

Of the many investigations carried out on the use of sulfanilamide against simian malaria the greatest number have been against Pl Knowlesi infections In view of the fact that almost all the sulfonamide drugs which have been tried against Knowlesi are beneficial it seems apparent that although this organism is extremely virulent to monkeys it is extremely susceptible to chemotherapy.

Singh and Singh (45) and Rodhain (44) report on the effectiveness of sulfanilamide against Pl Khowlesi in monkeys (rhesus) in both acute and chronic infections

Coggeshall (14) (15) states that sulfanilamide has prophylactic value and marked therapeutic effect on acute Pl Knowlesi

infections in rhesus monkeys The dosage which he used was 3 0 grams given intraperitoneally. This was enough to render the blood of the monkeys non-infectious.

Against Pl Inui, however, sulfanilamide is quite ineffective Coggeshall (16) treated both rhesus and cynamolgos monkeys having mixed Knowlesi and Inui infections with sulfanilamide The Knowlesi infection was very quickly eradicated whereas the milder Inui infection was not touched.

Rodhain (44) also tried the effect of sulfanilamide in chimpanzees infected with Pl reichenovi, a parasite somewhat related to Pl Falciparum He reported the drug to be quite effective.

3 Sulfanilamide in Avian Malaria.

Walker (51) published a negative report for sulfanilamide against Pl relictum in birds Coggeshall (15) also reported negative results against Pl Cathemerium in canaries and Pl Lophurae in chicks.

4. Sulfanilamide in In-Vitro Tests

Coggeshall (15) (16) has tried sulfanilamide in vitro against Pl Knowlesi and Pl Inui He found by Warburg studies that Pl Knowlesi parasites use approximately six times as much oxygen in their metabolic processes as an equal number of Pl Inui parasites Addition of sulfanilamide to the cells practically eliminated the respiration of Pl Knowlesi without having any effect whatsoever on Pl Inui

(b) Sulfapyridine in Malaria

1 Sulfapyridine in Human Malaria.

Two reports are available on the use of sulfapyridine against Pl Vivax malaria Chopra et al (13) treated seven cases with 0 5 gram doses given three times daily for five days followed by 1 0 grams four times daily thereafter They found that both the sexual and asexual forms of the parasite disappeared from the peripheral blood stream in from three to six days. Pakenham-Walsh and Rennie (41) tried the drug on induced tertian malaria, administering three grams daily The infection cleared up but relapses were noticed.

Against Falciparum (malignant tertian) malaria sulfapyridine was found effective in four cases by Chopra et al (13) The dosage was 0 5 gram three times daily for five days and then 1 0 grams four times daily. Under this treatment the asexual forms (schizonts) were eradicated from the blood in from three to six days

The same worker (13) tried the same treatment on one case of quartan malaria. In this case the parasites were found to persist for two days after the treatment was ended and the patient soon relapsed.

2. Sulfapyridine in Simian Malaria

Singh and Singh (45) found that administration of 3 grams of sulfapyridine daily until a total of about 26 grams had been given sufficed to render the blood of monkeys free from parasites

and to eradicate the infection Chopra and Das Gupta (11) indicated that doses of sulfapyridine much less than would be used proportionately for man namely 0 13 grams intramuscularly in oily suspension for a five kilogram monkey, caused the destruction of Pl Knowlesi parasites

3 Sulfapyridine in Avian Malaria

Walker (51) reports sulfapyridine to be ineffective against Pl relictum in birds

(c) Sulfathiazole in Malaria

1 Sulfathiazole in Human Malaria

Only one investigator has reported on the use of this drug Pakenham-Walsh (42) disclosed the successful treatment of Vivax malaria using 2 grams of drug three times daily at intervals of four hours

(d) Prontosil in Malaria

1 Prontosil in Human Malaria

Chopra et al (12) and Pakenham-Walsh and Rennie (41) obtained positive results against Pl. Vivax malaria with Prontosil The former administered 3-4 grams of drug daily for five days This treatment caused disappearance of both the sexual and asexual forms of the parasite from the peripheral blood The latter investigators used 3 grams of Prontosil per day and obtained eradication of parasites within three weeks

On the other hand Read and Pino (43) state that prontosil has no practical chemotherapeutic value in Vivax malaria This observation was corroborated by Van der Wielen (50) and Menk and Mohr (33) The last named workers reported no success at all in tertian malaria from the administration of 2 tablets of Prontosil Rubrum three times daily

Against Falciparum malaria there is an equal division in reported results Chopra et al (12) claim disappearance of the schizonts from the blood after 5 days of treatment involving use of 3-4 grams of Prontosil daily Menk and Mohr (33) on the contrary report no success was derived from 2 tablets taken 3 times daily

Faget Palmer and Sherwood (24) obtained negative results from Prontosil against Pl Malariae Chopra et al (12) found that both the sexual and asexual form of the parasite were eliminated by the use of 3-4 grams of drug daily for five days and Van der Wielen (50) treated two cases of quartan malaria with 6 tablets of Prontosil per day and reported that the plasmodia disappeared from the blood and the temperature was reduced to normal very soon after the drug was given

2 Prontosil in Avian Malaria

Africa Dy and Soriano (1) report success in the treatment of praecox infections Ten birds infected with Pl praecox were treated with Prontosil by injection into the breast muscle Untreated birds were maintained as controls In the treated birds the parasites completely disappeared whereas they persisted in the controls.

Chopra and Basu (10) found that even heavy doses of Prontosil (40 tablets) were unable to prevent the subsequent develop-

ment of crescents in Anopheles Stephensi

(e) Prontosil Soluble in Malaria
1 Prontosil Soluble in Human Malaria

Menk and Mohr (33) obtained negative results with Prontosil Soluble using 5 cc. of a 5% solution given intramuscularly per day Hall (27) reports uncertain results on four cases of Vivax malaria where the drug was given with Prontylin (40 grams) in doses of 10 cc. every four hours On the other hand Hill and Goodwin (28) (29) claimed successful treatment of seven cases of Pl vivax malaria with four injections of 10 cc of a 2 5% solution of Prontosil Soluble at intervals of twelve hours Read and Pino (43) used Prontosil Soluble intramuscularly in place of Prontosil in Vivax malaria wherever vomiting occurred The results attributable to this drug are indefinite although the general conclusion reached from all drugs used in this investigation is negative.

Against Pl Falciparum one report, Hall (27) is negative and one report Hill and Goodwin (28) (29) is positive The latter workers treated 90 cases of Falciparum malaria with 10 cc of the drug (2 5%) every 12 hours intramuscularly with beneficial results

There appears to be no reports on the use of Prontosil Soluble against Pl malariae

2 Prontosil Soluble in Simian Malaria

Das Gupta and Chopra (17) used heavy doses of Prontosil Soluble (3 cc -n weights given) in monkeys (Silenus Rhesus) infected with Pl Knowlesi They reported that the drug has a definite action on plasmodia, much more like the action of quinine than atebrin, but that there is no advantage over quinine These investigators pointed out that small doses (0 5-1 cc) of the drug completely failed to check the plasmodia whereas 3 cc is effective On this basis they intimate that earlier reports on the failure of the sulfonamide drugs may have been due to the dosage being too light

(f) Uliron in Malaria
1 Uliron in Human Malaria

The only report available on the use of Uliron against malaria is that of Loennecken (32) who found that the drug had no action against benign tertian malaria

(g) Soluseptasine in Malaria
1 Soluseptasine in Human Malaria

The results attained by the use of this compound against Vivax malaria are promising Farinaud and Eliche (25) and Farinaud and Ragiot (26) report that Soluseptasine in doses of 10 cc given twice daily intravenously showed remarkable schizonticidal power, causing disappearance of this form from the peripheral blood The gametes, however, were not similarly affected This general result is corroborated by Durand and Villain (23) who successfully treated two cases of Vivax malaria with 15 cc given intramuscularly twice daily.

The reports on Soluseptasine as a chemotherapeutic agent against Pl Falciparum are also favorable Farinaud and Ragiot (26) achieved positive results on a patient by the use of 10 cc given

twice daily On the sixth day the schizonts had disappeared, however, some increase was noted in the number of gametes Farinaud and Eliche (25) point out that this drug does not affect the sexual forms of Pl Falciparum

Against Pl malariae the results are substantially as reported by Farinaud and Ragiot (26) for Pl Falciparum, schizonticidal action but not gametocidal power

2 Soluseptasine in Simian Malaria

Chopra and Das Gupta (9) used 2 cc of a 5% solution of the above drug intravenously followed by a similar dose given intramuscularly Full recovery is reported within 24 hours

(h) Rubiazole in Malaria

1 Rubiazole in Human Malaria

Rubiazole was the first of the sulfonamide drugs to be reported in the treatment of malaria Diaz de Leon (19) obtained successful results in fifteen cases of Pl Vivax infection The treatment he used comprised two tablets of Rubiazole Rousse given three times daily until the symptoms abated followed by one tablet daily to complete the cure This result was corroborated by Barreras (3) who successfully treated eight cases of Vivax malaria in Havana with Rubiazole Durand and Villain (23), however, obtained indifferent results in tertian malaria from the use of 8 tablets (0 5 gram) per day Out of two cases one was cured and one was not

Against Pl Falciparum some of the same workers namely Barreras (3) and Durand and Villain (23) present an indefinite picture as to the efficacy of Rubiazole Barreras reports no action while Durand and Villain obtained indeterminate results from the use of 8 (0 5 gram) tablets daily in four cases Only two were cured.

Durand and Villain (23) report indefinite results against Pl malariae Morones (35) published a report on the use of Rubiazole but details are not available, and Diaz de Leon (20) pointed out that a large dosage of sulfonamide drugs is necessary to obtain results

2 Rubiazole in Simian Malaria

Durand and Villain (23) report that Rubiazole has definite action against Pl Knowlesi

3 Rubiazole in Avian Malaria

Durand and Villain (23) tried Rubiazole against Haemoproteus Columbae infections in pigeons without success

(i) Proseptasine in Malaria

1 Proseptasine in Human Malaria

Motzfeldt (36) a case report on two cases of human malaria treated with Proseptasine One grain of drug was given three times daily This treatment caused prompt abatement of the fever and rapid disappearance of the parasites but relapses occurred.

Durand and Villain (23) treated Vivax infections with

doses of four to six tablets per day The results were fair, out of six cases four were successfully cured Pakenham-Walsh and Rennie (40) used three grams of the drug daily and obtained eradication of the parasites in about three weeks

Against Falciparum malaria Sinton, and Sinton, Hutton and Shute (46) (47) state that Proseptasine has a prophylactic value. Oral doses of two grams of drug three times daily for one day followed by a further dose of 1 5 grams the next day were given to 8 patients Following this each patient was bitten by fifteen mosquitoes (A maculipennis) infected by Pl Falciparum Four hours later a further dose of 2 5 grams of drug was given and 2 0 grams after another four hours. The patients were observed for seven days without signs of infection Durand and Villain (23) published results indicating that the drug is useful against malignant tertian malaria Five patients were successfully treated with the drug. Against Pl malariae the results are quite indefinite

2 Proseptasine in Simian Malaria

Durand and Villain (23) report success in the treatment of Pl Knowlesi infections.

3 Proseptasine in Avian Malaria

Durand and Villain (23) used the drug unsuccessfully against Haemoproteus infections in pigeons

(j) Sulfanilyl Sulfanilate in Malaria

1 Sulfanilyl Sulfanilate in Simian Malaria

Coggeshall (15) found that doses of 3 grams intraperitoneally were valueless against Pl Knowlesi infections in monkeys

2 Sulfanilyl Sulfanilate in Avian Malaria

Coggeshall (15) found this drug to be useless against Pl Lophurae in chicks and Pl Cathemerium in canaries

(k) Rodilone in Malaria.

1 Rodilone in Human Malaria

The sole report on the use of a sulfone against malaria is that of Durand and Villain (23) who treated five patients with Pl. Vivax infections with 4 to 8 tablets of Rodilone (diacetyldiaminodiphenylsulfone) and obtained one cure, two failures and two *partial improvements*

(l) Naphthalene Sulfonamide in Malaria

1 2-Amino Naphthalene-6-Sulfonamide in Avian Malaria

Walker (51) prepared the above compound and reported it to be inactive against Pl relictum in birds.

(m) N^1,N^4-Substituted Sulfanilamides in Malaria

Walker (51) prepared a series of N^4-substituted and

N^1 N^4-substituted sulfanilamides including examples in which the dialkvlaminoalkylamino chains common to both the Plasmochin type and Atebrin type compounds were attached in the N^4-position None of these compounds were active against Pl relictum in birds Drosdov and Stavrovskaya (22) prepared a similar series of compounds with the major difference that in their case the dialkylaminoalkylamino groups were also attached in the N^1-position They also report no activity against bird malaria The latter workers also prepared dialkylaminoalkylamino compounds analogous to Prontosil and Prontosil Soluble but obtained no evidence of activity

Under this classification, may also be placed the cinchonine sulfanilamide and quinine sulfanilamide combinations tested by Stuart et al (49) against Pl relictum in canaries These combinations were found to have about the same activity to be expected from the use of a corresponding weight of the alkaloid alone Large doses caused a lag in the rate of appearance of the parasites similar to that caused by quinine.

(n) Acridine Sulfonamides in Malaria

In the above series of compounds the sulfanilamide nucleus was modified by substitution thereon of parts of the Plasmochin and Atebrin anti-malarials

Another mode of attack is represented by the preparation of Acridine nuclei modified by sulfonamido or sulfanilamido groups (18)

Mietzsch and Mauss (34) patented a series of Acridine compounds of the Atebrin type in which sulfonalkyl amino groups were attached in the 2 or 7 positions No pharmacological tests are given

This same line of attack was followed by Basu and Das Gupta (4) who also reported no pharmacological tests

A series of sulfanilamido substituted acridines were prepared by Basu and Das Gupta (4) using standard methods of preparation but here again no tests are cited

(o) Quinoline Sulfonamides

In 1935 Boguslaw and Bobranski (5) prepared a series of quinolines having sulfanilamido groups attached thereto via the N^1 and N^4 positions No therapeutic tests in these compounds are given Although not specifically cited as antimalarials they are included to indicate the compounds of this type which have been prepared for therapeutic applications

III Reviews on Sulfonamido Drugs in Malaria

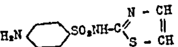
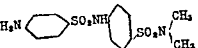
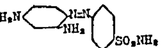
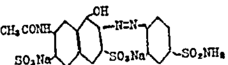
Brief reviews which include or relate to the use of sulfonamido compounds in the treatment of malaria have been published by Buttle (7), Anderson (2) and in the Brit Med Journ (6).

IV Table I

In this table the symbol + means the compound was active, ± the result was indefinite and- the results were negative The reference numbers refer to the bibliography at the end of Part II

Name and Formula	Parasite	Host	Action	References
	Pl Vivax	Human	+	(30) (52)
	Pl Vivax	Human	±	(48)
	Pl Vivax	Human	-	(24) (27) (32) (37) (38) (43) (23)
	Pl Falciparum	Human	±	(23) (37) (38)
	Pl Falciparum	Human	-	(24)
	Pl Malariae	Human	±	(37) (38)
$H_2N-C_6H_4-SO_2NH_2$	Pl Knowlesi	Human	+	(16)
Sulfanilamide	Pl Knowlesi	Simian	+	(14) (15) (16) (44) (45)
	Pl Inui	Simian	-	(16)
	Pl Reichenovi	Simian	+	(44) (7)
	Pl Relictum	Avian	-	(7) (50)
	Pl Cathemerium	Avian	-	(7) (15)
	Pl Lophurae	Avian	-	(7) (15)
	Pl Knowlesi	In Vitro	-	(14) (15) (16)
	Pl Inui	In Vitro	-	(16)
	Pl Vivax	Human	+	(13)
$H_2N-C_6H_4-SO_2NH-C_5H_4N$	Pl Vivax	Human	±	(41)
	Pl Falciparum	Human	+	(13)
	Pl. Malariae	Human	-	(13)
Sulfapyridine	Pl Knowlesi	Simian	+	(11) (45)
	Pl Relictum	Avian	-	(51)

(continuation)
Table I

Name and Formula	Parasite	Host	Action	References
 Sulfathiazole	Pl Vivax	Human	+	(42)
 Uleron	Pl Vivax	Human	-	(32)
 Prontosil	Pl Falciparum	Human	-	(33)
	Pl Vivax	Human	+	(12) (33)
	Pl Falciparum	Human	+	(12)
	Pl Malariae	Human	+	(45) (12) (50)
	Pl Praecox	Avian	+	(1)
	Pl Malariae	Human	-	(24)
	Pl Vivax	Human	-	(43)
	Pl Vivax	Human	-	(33) (50)
	Crescents	Mosquito	-	(10)
 Prontosil Soluble	Pl Vivax	Human	+	(28) (29)
	Pl Falciparum	Human	+	(28) (29)
	Pl Vivax	Human	-	(33)
	Pl Knowlesi	Simian	+	(17)
	Pl Falciparum	Human	-	(33)
	Pl Vivax	Human		(27)
	Pl Falciparum	Human		(27)

(continuation)
Table I

Name and Formula	Parasite	Host	Action	References
Soluseptasine	Pl Vivax	Human	+	(26) (25)
	Pl Vivax	Human	+	(23)
	Pl Knowlesi	Simian	+	(9)
	Pl Falciparum	Human	+	(26) (25)
	Pl Malariae	Human	+	(26)
Rubiazole	Pl Malariae	Human	±	(23)
	Pl Vivax	Human	+	(19) (3)
		Human	±	(23)
	Pl Falciparum	Human	±	(23)
	Pl Falciparum	Human	-	(3)
	Haemoproteus Columbae	Avian	-	(23)
	Pl Knowlesi	Simian	+	(23)
Proseptasine (Septazine)	Pl Vivax	Human	±	(23)
	Pl Falciparum	Human	+	(23) (46) (47)
	Pl Relictum	Avian	-	(7)
	Pl Vivax	Human	+	(40)
	Pl Malariae	Human	±	(23)
		Human	±	(36)
	Haemoproteus Columbae	Avian	-	(23)
	Pl Knowlesi	Simian	+	(23)
Rodilone	Pl Vivax	Human	±	(23)

(continued)

Table 1

Name and Formula	Parasite	Host	Action	References
H_2N-naphthalene-SO_2NH_2 2-Amino Naphthalene-6-Sulfonamide	Pl Relictum	Canary	-	(51)
H_2N-C_6H_4-SO_2NH-C_6H_4-SO_3H Sulfanilyl Sulfanilic Acid	Pl Knowlesi Pl Cathemerium Pl Lophurae	Simian Canary Chick	- - -	(15) (15) (15)
Cinchonine-Sulfanilamide Complex	Pl Relictum	Avian	+	(49)
Quinine-Sulfanilamide Complex	Pl Relictum	Avian	+	(49)
$NHCOCH_3$-C_6H_4-$SO_2NHCH_2CHOHCH_2$-N<$(CH_2$-$CH_2)_2$>CH_2 4-Acetaminobenzol(γ-piperidino) β-oxypropyl) Sulfonamide		Avian	-	(22)

(continued)

(continuation)
Table I

Name and Formula	Parasite	Fost	Action	References
NH_2-C_6H_4-$SO_2NHCH_2CHOHCH_2N\langle(CH_2-CH_2)_2\rangle CH_2$ 4-Aminobenzol (γ-piperidino β-oxypropyl) Sulfonamide		Avian	-	(22)
C_2H_5NH-C_6H_4-SO_2NH_2 N^4-Ethyl Sulfanilamide	Pl Relictum	Avian	-	(51)
C_2H_5-N(CHO)-C_6H_4-SO_2NH_2 N^4-Formyl-N^4-Ethyl Sulfanilamide	Pl Relictum	Avian	-	(51)
$(C_2H_5)_2NCH_2CH_2NH$-C_6H_4-$SO_2N(CH_3)_2$ N^4,β-diethylaminoethyl N^1-Dimethyl Sulfanilamide	Pl Relictum	Avian	-	(51)

(continued)

(continued)
Table I

Name and Formula	Parasite	Host	Action	References
$(C_2H_5)_2NCH_2CH_2NH-C_6H_4-SO_2N(C_2H_5)_2$ N^4, β-diethylaminoethyl N^1-Diethyl Sulfanilamide	Pl Relictum	Avian	-	(51)
$(C_2H_5)_2NCH_2CH_2NH-C_6H_4-SO_2NH-CH-CH_2-CH_2-CH_2-CH_2$ N^4, β-diethylaminoethyl N^1-Pentamethylene Sulfanilamide	Pl Relictum	Avian	-	(51)
$(C_2H_5)_2NCH_2CH_2CH_2NH-C_6H_4-SO_2N(C_2H_5)_2$ N^4, γ-diethylaminopropyl N^1-Diethyl Sulfanilamide	Pl Relictum	Avian	-	(51)

(continuation)
Table I

Name and Formula	Parasite	Host	Action	References
$NHCOCH_3$ (benzene ring) $SO_2NHCH_2CH(OH)CH_2N(C_2H_5)_2$ 4-Acetylaminobenzol (γ-diethylamino-β-oxypropyl) Sulfonamide		Avian	-	(22)
NH_2 (benzene ring) $SO_2NHCH_2CH(OH)-CH_2N(C_2H_5)_2$ 4-Aminobenzol (γ-diethyl amino-β-oxypropyl) Sulfonamide		Avian	-	(22)
$NHCOCH_3$ (benzene ring) $SO_2NHCH(CH_3)CH_2CH_2CH_2N(C_2H_5)_2$ 4-Acetylaminobenzol(γ-diethyl amino-α-methylbutyl) Sulfonamide		Avian	-	(22)

(continued)

(continuation)
Table I

Name and Formula	Parasite	Host	Action	References
NH_2 (benzene ring) $SO_2NHCH(CH_3)CH_2CH_2CH_2N(C_2H_5)_2$ 4-Aminobenzol (γ-diethylamino-α-methylbutyl) Sulfonamide		Avian	-	(22)
$(C_2H_5)_2NCH_2CH_2CH_2NH$ (benzene ring) SO_2NH_4 4(γ-diethylaminopropyl) amino benzol Sulfonamide		Avian	-	(22)
(naphthalene ring, OH) $N=N$ (benzene ring) $SO_2NHCH(CH_3)CH_2CH_2N(C_2H_5)_2$ 4'(γ-diethylamino-α-methyl butyl) sulfonamido benzol azo-2-oxy naphthalene		Avian	-	(22)

(continued)

(continuation)
Table I

Name and Formula	Parasite	Host	Action	References
N=N– ; OH NH_2 ; SO_3Na ; SO_3Na ; $SO_2NHCHCH_2CH_2CH_2N(C_2H_5)_2$; CH_3 4'(γ-diethylamino-α-methyl butyl) sulfonamido benzol azo-1-oxy-8-*amino-3,6-naphthalene disulfonic* acid sodium salt		Avian	-	(22)
$NHCOCH_3$; SO_2NH ; CH_3 ; $SO_2NHCHCH_2CH_2CH_2N(C_2H_5)_2$ 4(4'-Acetaminobenzol sulfonamido) benzol(γ-diethylamino-α-methyl butyl) Sulfonamide.		Avian	-	(22)

(continuation)
Table I

Name and Formula	Parasite	Host	Action	References
$NHCH_2CH_2CH_2N(C_2H_5)_2$ / $SO_2NHCH(CH_3)CH_2CH_2CH_2N(C_2H_5)_2$ 4(γ-diethylaminopropyl)amino benzol(γ-diethylamino-α-methyl butyl) Sulfonamide		Avian	-	(22)
$N{=}N$–(2,4-diamino phenyl) NH_2, NH_2 / $SO_2NHCH(CH_3)CH_2CH_2CH_2N(C_2H_5)_2$ 4(γ-diethylamino-α-methylbutyl) sulfonamido-2,4-diamino azo benzol		Avian	-	(22)
CH_3O–acridine–$NH-CH_2-CH(OH)-CH_2-N(C_2H_5)_2$; $SO_2N(CH_3)_2$ 2-Methoxy-7-sulfondimethylamido 9(α-diethylamino-β-oxy-γ-propyl amino) acridine				(34)

(continued)

(continuation)
Table I

Name and Formula	Parasite	Host	Action	References
$(CH_3)_2NO_2S$–, $NHCH_2CHOHCH_2N(C_2H_5)_2$, –$CH_3$, N 2-Sulfondimethylamido-6-methyl 9(α-diethylamino-β-oxy-γ-propyl amino) acridine				(34)
CH_3O, $NHCH_2CH_2$–$N(C_2H_5)_2$, $SO_2N(C_2H_5)_2$, N 2-Methoxy-7-sulfondiethylamido 9(α-diethylaminoethylamino) acridine				(34)
$(CH_3)_2NO_2S$–, NH, –OCH_2CH_2–$N(C_2H_5)_2$, CH_3, N 2-Sulfondiethylamido-7-methyl 9(p-diethylaminoethoxyphenyl amino) acridine				(34)

(continued)

(continuation)
Table I

Name and Formula	Parasite	Host	Action	References
2-Sulfondimethylamido-7-methyl 9(p-aminomethylphenylamino) acridine				(34)
2-Sulfonamido-7-methoxy 5(ω-diethylamino isoamyl) amino acridine				(4)
2-Sulfonamido-7-methoxy 5(δ-diethylaminobutyl) amino acridine				(4)

(continued)

(continuation)
Table I

Name and Formula	Parasite	Host	Action	References
$NHCH(CH_3)CH_2CH_2CH_2N(C_2H_5)_2$; CH_3O—; —SO_2NH_2; N 3-Sulfonamido-7-methoxy 5(ω-diethylamino isoamyl) amino acridine				(4)
$NHCH(CH_3)CH_2CH_2CH_2-N(C_2H_5)_2$; CH_3O—; —$SO_2N(C_2H_5)_2$; N 3-Sulfondiethylamido-7-methoxy 5(ω-diethylamino isoamyl) amino acridine				(4)
$NHCH_2CH_2CH_2CH_2-N(C_2H_5)_2$; CH_3O—; —$SO_2N(C_2H_5)_2$; N 3-Sulfondiethylamido-7-methoxy 5(√-diethylaminobutyl) amino acridine				(4)

(continued)

(continuation)
Table I

Name and Formula	Parasite	Host	Action	References
CH_3 $NHCHCH_2CH_2CH_2-N(C_2H_5)_2$; C; CH_3O-; $-SO_2NH-$; N 3-Sulfonphenylamido-7-methoxy 5(ω-diethylamino isoamyl) amino acridine				(4)
$NHCH_2CH_2CH_2CH_2N(C_2H_5)_2$; C; CH_3O-; $-SO_2NH-$; N 3-Sulfonphenylamido-7-methoxy 5(ω-diethylaminobutyl) amino acridine				(4)
CH_3 $HNCH(CH_2)_3N(C_2H_5)_2$; H_2NO_2S-; $-NHSO_2-$; $-OCH_3$; N 3-Sulfonyl(p'-sulfonamido phenyl) amino-7-methory-5(ω-diethyl amino isoamyl) amino acridine				(18)

(continued)

(continuation)
Table I

Name and Formula	Parasite	Host	Action	References
H_2NO_2S-C6H4-$NHSO_2$- acridine ring with $HN(CH_2)_4N(C_2H_5)_2$ and OCH_3 substituents 3-Sulfonyl(p-sulfonamido phenyl) amino-7-methoxy-5(ω-diethylamino butyl) amino acridine				(18)
Et_2NO_2S-C6H4-$NHSO_2$- acridine ring with $HNCH(CH_3)(CH_2)N(C_2H_5)_2$ and OCH_3 substituents 3-Sulfonyl(p-sulfondiethylamido phenyl) amino-7-methoxy 5(ω-diethylamino isoamyl) amino acridine				(18)
Et_2NO_2S-C6H4-$NHSO_2$- acridine ring with $HN(CH_2)_4N(C_2H_5)_2$ and OCH_3 substituents 3-Sulfonyl(p-sulfondiethylamido phenyl) amino-7-methoxy-5(ω-diethylaminobutyl) amino acridine				(18)

(continued)

(continuation)
Table I

Name and Formula	Parasite	Host	Action	References
Et_2NO_2S-C₆H₄-$NHSO_2$-acridine with $HN(CH_2)_3N(C_2H_5)_2$ and OCH_3 substituents 3-Sulfonyl(p-sulfondiethylamidophenyl) amino-7-methoxy-5(γ-diethylaminopropyl) amino acridine				(18)
$(C_2H_5)_2NSO_2$-C₆H₄-$NHSO_2$-C₆H₄-NH_2 N^4-Sulfanilyl-N^1-Diethyl Sulfanilamido				(18)
Cl-acridine with NH-C₆H₄-SO_2NH-C₆H₄-$SO_2N(C_2H_5)_2$ and OCH_3 substituents 2-Chlor-7-methoxy-5(N^4-Sulfanilyl-N^1-Diethyl Sulfanilamide), Acridine				(18)
Cl-acridine with NH-C₆H₄-SO_2NH-C₆H₄-$SO_2N(C_2H_5)_2$ and CH_3 substituents 2-Chlor-7-methyl-5(N^4-Sulfanilyl-N^1-Diethyl Sulfanilamide), Acridine				(18)

(continued)

V Table II

Trade Name	Chemical Name	Formula
Albucid	N[1]-Acetylsulfanilamide	$H_2N\langle\ \rangle SO_2NHCOCH_3$
Aldanil	Sodium Formaldehyde-Sulfoxylate Derivative of Sulfanilamide	$NaOSOCH_2NH\langle\ \rangle SO_2NH_2$
Azosulfamide	see Neo Prontosil	
Cioagen 4	Calcium Di-sulfapyridina	$(H_2N\langle\ \rangle SO_2N\langle N \rangle)_2Ca$
Coccoclase	see Sulfapyridine	
Colsulanyde	see Sulfanilamide	
Dagenan	see Sulfapyridine	
Deseptyl	Sulfanilamide	
Diseptyl A(DB90)	Uleron	
Diseptyl B(DB87)	N[1]-Methyl-N[4]-Sulfanilyl Sulfanilamide	$H_2N\langle\ \rangle SO_2NH\langle\ \rangle SO_2NHCH_3$
Diseptyl C	Di-sulon	
Disulon	N[4]-Sulfanilyl Sulfanilamide	$H_2N\langle\ \rangle SO_2NH\langle\ \rangle SO_2NH_2$
Estreptocida	Sulfanilamide	
Eubasinum	Sulfapyridine	
Eubasin	Sulfapyridine	
1162F	Sulfanilamide	
Lysamide	Aluminum Sulfanilamide	$(H_2N\langle\ \rangle SO_2NH)_2Al\ 5H_2O$
Lysococcine	Sulfanilamide	
M and B 693	see Sulfapyridine	
Neoprontosil	see Prontosil Soluble	
Novamide	N[4]-(Sodium Sulfomethylene) Sulfanilamide	$NaO_3SCH_2NH\langle\ \rangle SO_2NH_2$
Promin	Sodium Salt of p,p'-Di-amino Di-phenyl Sulfone-N,N-Glucose Sulfonate	$NaO_3SCHHN\langle\ \rangle SO_2\langle\ \rangle NH\text{-}CH\text{-}SO_3Na$, with $(CHOH)_4$ CH_2OH under each end

(continuation)
Table II

Trade Name	Chemical Name	Formula
Prontosil	2,4-Diazo Amino Azo Benzene-4'-Sulfonamide	H_2NO_2S-C6H4-N=N-C6H3(NH_2)-NH_2
Prontosil Album	see Sulfanilamide	
Prontosil Flavum	see Prontosil	
Prontosil S(oluble)	Di-sodium-4-Sulfamido Phenyl-2-Azo-7-Acetylamino-1-Hydroxy Naphthalene-3,6-Di-sulfonate	H_2NSO_2-C6H4-N=N-, OH, -$NHCOCH_3$, NaO_3S-, -SO_3Na
Prontylin	see Sulfanilamide	
Proseptazine	see Septazine	
Pyriamid	see Sulfapyridine	
Rodilone	4,4'-Di-acetyl Diamino Di-sulfone	CH_3CONH-C6H4-, CH_3CONH-C6H4-, SO_2
Rubiazole	6'-Carboxy-2',4'-Di-amino-Azo Benzene-4-Sulfonamide	H_2NO_2S-C6H4-N=N-C6H2(NH_2)(COOH)-NH_2
Sanamide	see Sulfanilamide	
Septazine	N^4-Benzyl Sulfanilamide	C6H5-CH_2=N-C6H4-SO_2NH_2
Septoplex	see Sulfanilamide	
Soluseptazine	N^4-(Di-sodium-α,γ-Di-sulfo-γ-Phenyl Propyl)- Sulfanilamide	C6H5-CH(SO_3Na)-CH_2-CH(SO_3Na)-NH-C6H4-SO_2NH_2
Stramide	see Sulfanilamide	
Streptal Soluble	N^4-Quinolinyl Sulfanilamide	N, -COOH, -CONH-C6H4-SO_2NH_2
Streptal	see Sulfanilamide	
Streptamid	see Sulfanilamide	
Streptasol	N-Sulfanilyl Glycine	H_2N-C6H4-SO_2NHCH_2COOH
Streptocide	see Sulfanilamide	
Streptocid Album	see Sulfanilamide	
Streptocid Rubrum	see Neo Prontosil	
Streptozon	see Prontosil	
Streptozon S	see Prontosil Soluble	
Sulfacet	see Albucid	

(continuation)

Table II

Trade Name	Chemical Name	Formula
Sulfadiazine	2-Sulfanilamido Pyrimidine	$H_2N\langle\,\rangle SO_2NH-C\begin{matrix}N=CH\\N=CH\end{matrix}CH$
Sulfamethyldiazine	2-Sulfanilamido-4-Methyl Pyrimidine	$H_2N\langle\,\rangle SO_2NH-C\begin{matrix}N=CH\\N=C(CH_3)\end{matrix}CH$
Sulfamidyl	see Sulfanilamide	
Sulfanilamide	Sulfanilamide	$H_2N\langle\,\rangle SO_2NH_2$
Sulfanilamide E O S	Sulfanilamide N^4-Sodium Ethyl Sulfonate	$CH_3-CH(SO_3Na)-NH-\langle\,\rangle-SO_2NH_2$
Sulfapyridine	2-Sulfanilamido Pyridine	$H_2N\langle\,\rangle SO_2NH\langle N\rangle$
Sulfathiazole	2-Sulfanilamido Thiazole	$H_2N\langle\,\rangle SO_2NH-C\begin{matrix}S-CH\\N-CH\end{matrix}$
Sulfaphenylthiazole	2-Sulfanilamido-4-Phenyl Thiazole	$H_2N\langle\,\rangle SO_2N(H)-C\begin{matrix}S-C(C_6H_5)H\\N-CH\end{matrix}$
Sulfonamide P	see Sulfanilamide	
Thiazamide	see Sulfathiazole	
Uleron(Uliron)	N^1,N^1,-Di-methyl-N^4-Sulfanilyl Sulfanilamide	$H_2N\langle\,\rangle SO_2NH\langle\,\rangle SO_2N\begin{matrix}CH_3\\CH_3\end{matrix}$
Ultraseptyl	2-Sulfanilamido-4-Methyl Thiazole	$H_2N\langle\,\rangle SO_2NH-C\begin{matrix}S-CH-CH_3\\N-CH\end{matrix}$

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CHEMOTHERAPY of MALARIA

Part III

Amidines as Antimalarials

by

James H Williams

June 1941

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General Discussion

The earliest reference in the literature directed to the use of amidino compounds as antimalarials is the work of Easson and Pyman (4) in 1931 These investigators tested three unrelated amidines (See Table I) against bird malaria without success

In 1937, however, the use of amidines was re-examined by King, Lourie and Yorke (9) who postulated their research on a theoretical background which later was shown to be false However, the results worked out all right despite the false premises on the basis of which the work was started

Yorke (16) outlines the factors which led to the investigation as follows

In 1911 Biot, Biot and Richard (1) had observed that trypanosomes require large amounts of glucose for proper metabolism Since, that time other workers had expanded on the work so that certain postulates were derivable therefrom These postulates were

1 The presence of glucose is necessary for the existance of trypanosomes

2 Trypanosomes in their metabolism consume relatively enormous ouantities of glucose

3 Laboratory animals experimentally infected with trypanosomes frequently exhibit during the course of the infection a certain degree of hypoglycemia but this is constantly present to a marked degree in the agonal period of the disease or in the stage immediately preceding it

4 The mechanism whereby hypoglycemia is produced is still uncertain

In 1936, Schern and Artagaveyta-Allende (15) demonstrated that synthalin (decamethylene diguanidine) has a definite action on T equinum and concluded that the effect must be due to an effect on the blood sugar, producing hypoglucemia

This observation was checked by Lourie and Yorke (11) They found a powerful in vitro trypanocidal action, but observed that the dosage necessary to obtain hypoglucemia caused severe injury to the liver Furthermore, they found that insulin which causes hypoglucemia has no effect on the trypanosomes either in vitro or in vivo Accordingly, they concluded that the action must be direct

Following up this lead King Lourie and Yorke (9) carried out tests on a series of guanidines, amidines isothioureas and the like, prepared at the chemical laboratories of May & Baker in England (13)(14)

In view of the results obtained with trypanosores attention was also turned to the malarial parasite.

It was known (8) that feeding glucose to canaries infected with malaria resulted in an increase in the number of parasites protraction of the disease and usually lethal outcome The course of an initially low infection was substantially unchanged by intraperitoneal injection of insulin but flared up again when glucose was given

It was also known that humans suffered from hypoglucemia when first infected with malaria (10)

I Undecane Diamidine in Malaria

In view of this correlation between trypanosome diseases and malaria Glyn-Hughes, Lourie and Yorke (7) in 1938 tried the effect of undecane diamidine on Pl Vivax infections. They found that a man can be safely given 50 milligrams per day intravenously or 100 milligrams per day by mouth without toxic effects One half this dosage has a definite effect on Vivax malaria.

Christopher and Fulton (2) tried the effect of 1 11 undecane diamidine against Pl Knowlesi in Macacus rhesus monkeys using 2 5-5 0 milligrams per kilo of body weight administered by injection or twice this dosage when given by mouth They found that the drug has a definite action but that it causes toxic side reactions in the liver In canaries the toxic dose of this compound was found to be 0 2 milligram per 20 grams of body weight when given intraperitoneally or 0 6 milligram when given by mouth. The drug was found to cause liver damage and was ineffective against Pl relictum infections.

II Use of 4,4'-Diamidino Stilbene in Malaria

Fulton (6) investigated the effect of 4,4'-diamidino stilbene on malaria

In canaries infected by blood inoculation with Pl. relictum the toxic intraperitoneal dose of 4,4'-diamidino stilbene was 0 3 milligram or less, birds being unaffected by 4 to 5 times this dose by mouth The drug was given intraperitoneally four hours after infection and the dose repeated on five successive days This treatment, however, was unable to delay the appearance of parasites in the peripheral blood in doses near the maximum

Against simian malaria in doses of 5 milligram per kilo this drug had a definite action

Yorke (16) confirmed these observations and states that 4,4-diamidino stilbene is also effective against Pl Vivax and Pl falciparum in human malaria

[II 4,4'-Diamidino-1,5-Diphenoxy Pentane in Malaria

Fulton (6) and Yorke (16) report that 4,4'-diamidino-1,5-diphenoxy pentane is effective against Pl relictum in canaries, but the therapeutic index is small Repeated doses of 0 4 milligrams given intraperitoneally are well tolerated, the largest dose administered being 1 milligram This compound also has action against Pl Knowlesi in monkeys.

Table I

Name and Formula	Parasite	Host	Action	Reference
CH_3O-(ring, OCH_3)-$C(=NH)NH_2$ 3,4-Dimethoxy Benamidine		Avian	-	(4)
EtOOC-(ring)-$NH-C(=NH)-NH_2$ p-Carbethoxy Phenyl Guanidine		Avian	-	(4)
$H_2N-C(C_6H_5)=N-CH_2$-(ring, OCH_3)-OCH_3 Benzenyl Veratryl Amidine		Avian	-	(4)
$HN=C(H_2N)-(CH_2)_9-C(=NH)NH_2$ Undecane Diamidine	Pl Vivax Pl Knowlesi Pl Relictum	Human Simian Avian	+ + -	(7) (2) (2)

(continued

(Continuation)
Table I

Name and Formula	Parasite	Host	Action	References
$H_2N(HN{=})C-C_6H_4-CH{=}CH-C_6H_4-C({=}NH)NH_2$ (14) 4,4'-Diamidino Stilbene	Pl Knowlesi Pl Vivax Pl Falciparum Pl Relictum	Simian Human Human	+ + + -	(16) (6) (16) (16) (6)
$H_2N(HN{=})C-C_6H_4-O(CH_2)_5O-C_6H_4-C({=}NH)NH_2$ (15) 4,4'-Diamidino Diphenoxy Pentane	Pl Knowlesi Pl Relictum	Simian Avian	+ +	(16) (6) (16) (6)

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Search No. 893

CHEMOTHERAPY OF MALARIA

Part IV

Quinoline Compounds (exclusive of the Cinchona Derivatives) as Antimalarials

by

James H Williams

January 1942

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Quinoline Compounds as Antimalarials (Excluding the Cinchonas) - Part IV

Introduction

Since the elucidation of the constitution of the cinchona alkaloids by Skraup, Königs, von Miller, Rabe, etc. around 1906 until the war period of 1914-1918 the major trend in the investigation of quinoline compounds as anti-malarials was directed towards modifying the basic structure of quinine while maintaining the essential structure of the parent compound

During the last mentioned period, however, inability on the part of Germany, to import the necessary requirements of the naturally occurring cinchona alkaloids caused the I G Farbenindustrie to undertake researches having as their object the preparation of a synthetic substitute for the needed drug, quinine

Following the war the work was continued and in 1926 it was announced to the world that success had crowned the efforts of the I G. chemists in the synthesis of Plasmochin Several reports were published at once relating to the chemical and anti-malarial properties of the drug by Horlein (1926), Muhlens (1926), Roehl (1926) and Sioli (1926) but the exact constitution of the compound was not made available until some two years later (I G 1928).

The natural consequence attendant upon this disclosure of a new line of approach to the synthesis of quinoline compounds which would be active against malaria was that other groups of workers throughout the world were stimulated to take up the search along similar lines Fourneau and his Co-workers in France, Robinson, et al and Kermack and Co-workers in England, Magidson et al and Kritchevskii in Russia and Hegner and his Co-workers in the U S A. began to publish papers on quinoline anti-malarials of the Plasmochin type

It is not clear, from the literature, how much of the subsequent work in this field constituted a specific repetition of that already covered by the chemists of the I G Farbenindustrie since little of the work done at this last institution has ever been published in the journals Schulemann (1932) while discussing the general steps which led to the synthesis of Plasmochin made the statement that 12,000 compounds were studied before the structure providing the optimum therapeutic value was found Although this figure has been criticized by Fischl and Schlossberger (1933) as far too high, 1200 being much more plausible, it is certain that the amount of ground covered was enormous This is borne out by the fact that the I G Farbenindustrie was able to obtain extensive patent coverage throughout the world, on quinoline anti-malarials, which dominates and in many cases anticipates a high proportion of the work done later by others.

A review of the literature clearly indicates that by far the greatest amount of correlated research was centered around compounds closely related to Plasmochin, that is quinoline substituted in the 8 position by an alkylamino alkylene amino group and in the 6 position by an alkoxy group It is in this series that practically all the really effective anti-malarials of the quinoline type have thus far been found

Outside of this group no other series has shown much promise as a class although individual compounds therein may show activity

I Arrangement of the Search

To cover the total literature relating to quinoline antimalarials would be a task far beyond the requirements of our present necessity Fischl (1935) writes, for example that during the Years 1926 - 1935 alone there appeared over 700 papers relating to the clinical aspects of the treatment of malaria with Plasmochin Since such materials must of necessity be repetitious and since several reviews relating to Plasmochin are available such as those of Fischl and Schlossberger (1933), von Oettingen (1933), Findley (1939), Houben (1939) and the like, it has been deemed expedient to include herein only enough references on Plasmochin to provide the reader with an adequate picture of the drug as an anti-malarial

In connection with the literature relating to experimental work done on quinoline antimalarials it is possible to break it down into four separate divisions, namely, I Preparation of the compounds, II Methods used to test the compounds, III Results obtained and IV Correlation of structure with observed activity

In this report separate sections have been devoted to divisions II and IV Parts I and III are to be found in the form of tables No attention has been paid to the methods used to synthesize the compounds since they usually follow standard procedure Wherever convenient, notations have been made indicating the literature reference to the preparation of the drugs In addition references to many of the synthetic procedures used will be found in the section of the search devoted to a survey of the patent literature.

With reference to the review of compounds tested and results obtained, the data have been arranged in accordance with the positions taken by the substituents For example the 6 - 8 substituted quinolines are taken up first, followed by discussion, under individual headings, of compounds such as Plasmochin, Plasmocide, Dimeplasmin and the like, which have warranted further study on the basis of experimental results The relationship between structure and antimalarial activity then follows under its own heading

The same scheme has been followed with compounds having the substituents in other positions, with the exception that very little can be done in the way of correlating the results obtained.

To cover the patent literature a different procedure was followed for obvious reasons Here the information may be found in the form of brief abstracts or citations of claims

Separate bibliographics have been provided for the literature references and the patents, although the numbering has been made consecutive

The pages of the report are numbered to follow Part III of the Anti-Malarial search.

II Quinoline Antimalarials Prior to 1925

Occasional references may be found in the literature prior to 1925 concerning quinoline compounds, not related to the cinchona alkaloids, which have been claimed to have activity against the malarial parasite.

In this connection it may be noted that Moncorvo (1897) stated that 5-benzoylamino-8-ethoxy quinoline (Analgen) was effective against malaria Likewise, Mannaberg (1897) claimed success in the treatment of human malaria with 2-methyl-4-phenyl quinoline Quinosol or 8-oxy quinoline produced in 1895 has also been reported as having antimalarial properties (Fischl et al 1933). Einhorn (1890) prepared 2,4-dioxy-3,4-dihydro-6-methoxy quinoline which was later found to possess activity and Haüssler (1918) claimed that "Dippel's Oil", a bone distillate containing numerous quinoline compounds, was the best agent available for the treatment of intermittent fever.

Apart from the above, a relatively large number of quinoline derivatives have been tested for their action against paramoecia. It will be remembered from part I of this review that for some time the view was held that toxicity against paramoecia was a criterion of the activity of a compound towards protozoal organisms Consequently, much work was done, prior to the development of Roehl's method of testing for anti-malarial activity, on determining the action of possible anti-malarials against the paramoecium A complete review of such work would occupy more space than the subject warrants, however, it may be worth while to include a short section thereon later in the search.

In addition there is a class of quinoline compounds prepared as antimalarials prior to 1925 which are on the borderline between those represented in the present chapter and those closely allied to the cinchona group Such compounds will be included in that section of the review to be prepared later which will deal with the Cinchona like compounds

III Methods Used in Testing Antimalarials

As Hewitt (1940) points out in his book, the similarity of avian and human malaria is most strikingly demonstrated in their response to antimalarial drugs than in any other respect and Kikuth and Schönhofer (1935) attributed the quick discovery of Plasmochin and Atebrin to the availability of a suitable and reliable test means in avian malaria.

In view of the advantages inherent in the use of bird malaria it is not surprising that substantially all the experimental testing of quinoline compounds as anti-malarials has been carried out in this host

Roehl (1926) was the first worker to describe the action of a synthetic compound (Plasmochin), the antimalarial properties of which were revealed by tests on birds and which subsequently was found to be clinically effective against human malaria

In the Roehl test canaries were infected with Pl relictum by intramuscular inoculation with blood obtained from previously infected birds After such treatment it usually required from four to five days for parasites to appear in detectable quantities in the peripheral blood A number of these infected birds were maintained as controls and the remainder received treatment with the drug to be tested, each day for five to six days The effectiveness of the treatment was determined by the increase in the period within which parasites appeared in the peripheral blood as compared with the controls For example Roehl found that on treatment with quinine (1 800) in doses of 1 cc per 20 grams of bird body weight for six days the appearance of parasites was delayed and the period of retardation was raised to ten to twelve days Plasmochin acted similarly when given in concentration of 1 50,000

In the earlier attempts to test drugs on birds the compounds were administered subcutaneously However, Boyd (1926) introduced the use of the esophageal tube whereby compounds could be given by mouth with assurance that the entire dose would reach the stomach and this method was adopted by Roehl and others in much of the later work

For comparative purposes it is necessary to determine the chemotherapeutic index which is defined as follows

$$C\ I = \frac{\text{Minimum Effective Dose}}{\text{Maximum Tolerated Dose}}$$

Obviously it is practically impossible to obtain absolute values for the factors involved in determining this index, and so the usual procedure followed by the various workers has been to arbitrarily establish some point at which the action would be assumed to represent the minimum effective dose

Roehl, for example chose the smallest dose which showed definite delaying action as the minimum effective dose and obtained in this manner a value of 1/30 for the therapeutic index of Plasmochin

This method of arbitrarily choosing the results to be used to determine the effective dose enables a comparison to be made within the group of compounds tested by a single worker. However, one must be careful, in comparing the work of several individuals to give due consideration to the variations expected from the differences in technique used.

The method of Roehl either as originally designed by him, or with some modifications became the standard test for most of the later workers. For example, Hegner and Manwell (1927) used the method to check and confirm the results obtained by Roehl.

Likewise, Tate and Vincent (1933) used the method to test the antimalarial activity of a number of quinoline compounds which had been prepared by Robinson and his Co-workers The malarial parasite used in this

work was a strain of Pl relictum obtained from Roehl and the host was the common German roller canary (Serinus Canarius) The infection was transmitted by direct blood inoculation and the drugs were fed directly into the stomach in accordance with the method used by Roehl The only variation from the latter's technique arose from the fact that instead of a standard dose of 1 cc per 20 grams of bird body weight which he used Tate and Vincent gave 0 5 cc per 20 grams of bird body weight, the quantity of solution being increased or decreased in proportion as the weight of the bird was above or below the standard weight The routine of treatment corresponded to Roehl's, doses of the compound being given into the stomach on six consecutive days, the first dose coming four hours after the bird was inoculated Blood examinations were made daily until the tenth day and three times weekly thereafter until parasites appeared If no parasites were found for six weeks the birds were regarded as sterilized. Usually the maximum tolerated dose was first tried and the effective dose determined by working down from this value The therapeutic index was determined as the ratio described above

In discussing their results Tate and Vincent make the important observation that the time of administering the drugs in relation to the time of infection is of extreme importance, particularly if a comparison is to be attempted between the results of different workers For instance, they gave the first dose of drug four hours after inoculation whereas others preferred to wait until the next day

Fourneau et al (1930) published the results of their investigations on the antimalarial properties of a number of quinoline compounds using substantially the same method as Roehl These workers, however, made certain modifications in that the drugs were administered by mouth in admixture with a little moistened biscuit rather than by stomach tube. Furthermore, they defined the curative dose of drug as that at which slight activity was manifest Using this figure in determining the chemotherapeutic index of Plasmochin they obtained a value which was twice that obtained by Roehl

A year later Fourneau et al (1931) reported further on the testing of quinoline compounds for antimalarial activity, but this time they changed to the use of spontaneous Haemoproteus orizivorae infections in the Java Sparrow (French- Calfat, German- Reisvogel or Reisfinken) varieties Orizonis orizivora, Spermestes orizivora, Padda orizivora

In this paper Fourneau pointed out that the major variations in techniques used in testing antimalarials were based on the use of various parasites in different birds as for example

Pl relictum in Canaries
Proteosoma parasites in the Padda and Fringilla
Haemoproteus columbae in pigeons
Haemoproteus orizivorae in the Finch (Orizonis orizivora)

Of these the most used was the first However, the use of canaries involves a number of disadvantages which Fourneau et al decided could be avoided by the use of sparrows.

Birds of the variety Passeres are found in the natural state suffering from spontaneous Haemoproteus infections. Fourneau chose birds whose blood showed at least one parasite in fifteen fields of the microscope after being followed for five to six days In this way it was possible to be reasonably sure that the parasite count would not drop spontaneously to zero during the period of experimentation

The drugs were administered either by mouth in the case of insoluble compounds or sub-cutaneously in distilled water if the compound proved to be soluble In determining the dosage Fourneau first obtained the maximum tolerated dose and then arbitrarily chose test doses to correspond to $\frac{MTD}{4}$, $\frac{MTD}{10}$, $\frac{MTD}{40}$, etc

To follow the effect of medication, curves were plotted to show the day by day count of parasites in the blood and the curative dose was taken

as the smallest dose showing positive antimalarial action.

As may be expected from the arbitrary choice of dosage the chemotherapeutic index would not be the true index in the sense that Ehrlich conceived it. Absolute sterilization was never achieved and no attempt was made to determine the absolute minimum curative dose

The table below shows the comparison between the results obtained for Plasmochin by Fourneau in sparrows and in Canaries:

Data on Plasmochin

	M T D	Min Act Dose	C/T
Pl relictum (Canary)	0 00025	0 000004	1/60
Haemoproteus (Sparrow)	0 00016	0 000001	1/150 ±

Later, Fourneau et al (1933) expanded the use of Haemoproteus infections in the sparrow to determine the effect of varying the substituents in the quinoline ring Substantially the same method described above was followed with the exception that the chemotherapeutic index was taken as the coefficient

$$\frac{\text{Minimum Dose Curing in Five days}}{\text{Maximum Tolerated Dose}}$$

The dosages were expressed in grams per bird

Bovet, Benoit and Altman (1934) carried on similar studies using the same method as Fourneau et al (1933)

In discussing the use of the Haemoproteus infection in Sparrows Fourneau et al (1931) point out that quinine is quite inactive against this organism and offered as possible explanations (1) The fact that the infection in sparrows is essentially chronic as compared with the infections formerly used in canaries and (2) In the genus Haemoproteus only the gametes circulate in the peripheral blood, quinine being active only against the vegetative forms i e the schizonts and merozoites

On the basis then that Plasmochin shows results in both species of avian malaria it obviously has gametocidal power as compared with quinine and Atebrin which are highly active only in canaries.

It is clear as emphasized by Fourneau et al in their work that to obtain a chemotherapeutic index in any set of experiments, which may serve as a reliable criterion for comparison with the results obtained in any other set is a matter of considerable difficulty The results tend to vary considerably with the bird used, the parasite used, the techniques and predilections of the worker So much depends upon the competent judgment of the operator Accordingly, in attempting to make comparisons it becomes advisable to restrict oneself as far as possible to the results obtained in a single course of experiments or failing this to take into account differences in technique

Thus far the workers mentioned used canaries and sparrows The Russian school, however, did most of its work using Pl praecox infections in siskins Kritchevskii and Sternberg (1933) introduced this method, the species of bird used being Spinus spinus in the spring, summer and early autumn and Acanthus linaria in the late autumn and winter These birds are apparently more susceptible to malaria than canaries according to Sternberg (1934)

In carrying out the tests Kritchevskii and Sternberg gave the drugs sub-cutaneously, rather than orally and assumed as the maximum tolerated dose the largest daily dose of drug which the birds could stand for six consecutive days The minimal therapeutic dose was taken as the smallest dose of drug which retarded the incubation period from two to three days with respect to the control Using this method the C/T for Plasmochin was found to be 1/40

At this point the question arises as to the connection between

the results obtained with siskins, canaries and Sparrows From the discussion thus far it is clear that positive results in sparrows may be used to indicate the gametocidal power of drugs, whereas activity in canaries would tend to indicate schizonticidal action.

To appreciate the family relationships between the varieties of birds used in antimalarial work referencemay be made to Hewitt's work on Bird Malaria (1940)

In translating the work of the French school it should be noted that the frequently recurring word Calfat is apparently a colloquialism Fourneau et al (1931), however, helped to clarify the situation by citing the corresponding German names- Reisvogel or Reisfinken

The Reisvogel is the Paddy bird in English, also known as the Java Sparrown, varieties Orizonis orizivora, Spermestes orizivora and Padda orizivora.

As for the connection between canaries and siskins, Webster's Unabridged Dictionary indicates that both are finches the former being the variety serinus canaries and the latter spinus spinus The term finch, however, includes also birds of the family Fringillidae such as sparrows, grossbeaks, goldfinches, linnets, etc

Thus it may be gathered that artificially induced infections such as Pl relictum (Pl praecox) infections in birds of the finch type are susceptible to schizonticidal drugs while naturally occurring Haemoproteus infections in the Java Sparrow are susceptible to gametocidal drugs only

An entirely different method of attack to the problem of picking out anti-malarial drugs was elaborated by Hegner, Shaw and Manwell (1928) and Shaw (1928). The work of these men was based on the theory that a compound should be capable of penetrating the red blood cells in order to act upon the parasites. Accordingly, they studied the partition coefficients of a number of drugs, in totally unrelated classifications, between isotonic solutions and washed red cells suspended therein. The results obtained were then compared with the known antimalarial activity of the compounds

The technique used is described by Shaw (1928) Washed red cells were suspended in an isotonic solution (pH 7 4) containing concentrations of the compounds under test of about four parts in 10,000 The mixtures were agitated at room temperature for from 20 to 40 minutes, centrifuged from the red cells and the compound estimated by comparison, in an interferometer, with a control which contained only corpuscles and isotonic solution The diminution in concentration was considered as representing the amount of compound which had penetrated the red blood corpuscles. The results were calculated in terms of the partition coefficient between corpuscles and isotonic solution, considering the corpuscles as a separate immiscible phase

$$P = \frac{\text{Concentration in Corpuscles}}{\text{Concentration in Liquid}}$$

In order to definitely establish that the drugs were absorbed and not merely adsorbed, the treated cells were added to a fresh salt solution and again agitated Proof that the drug had actually penetrated the membrane lay in the fact that an equilibrium was again established entirely in accord with the partition coefficient previously determined

From the results obtained, the authors concluded that only those compounds which do not yield ions at the neutral point are absorbed, whereas compounds which are ionized at the neutral point are not capable of being absorbed.

Following the above studies various drugs which conformed to the above rule were tested in canaries infected with Pl cathemerium This particular parasite was chosen as against Pl praecox and Pl inconstans, which were also considered, on the basis that it has an asexual cycle of

24 hours and, consequently, daily smears would be comparable In addition higher types of infection may be established in birds using the chosen parasite

Infective inoculation of the birds was usually accomplished by intramuscular injection into the breast muscle or intraperitoneally In-travenous injections were avoided due to technical difficulties Drugs were given by mouth

The results obtained from these tests, however, gave no indication that absorption by red blood corpuscles was any criterion of drug activity

Considerable work has been done to determine the toxicity of quinoline drugs to paramoecia Brahmachari and his Co-Workers (1930-31) as well as Hegner, Shaw and Lanwell (1928) carried out studies along this line Although these tests may give preliminary indications of possible antimalarial activity they have not proved reliable (See later for additional discussion)

Tests have been conducted on the effect of quinoline antimalarials against many other organisms These will be indicated in the ensuing tables and will not be discussed in detail here Among these organisms, however, may be included Pl vivax Pl falciparum and Pl malariae in man, Halteridium infections in pigeons, Pl elongatum and Pl gallinaceum in birds and the like

One of the problems presented to the pharmacologist who is engaged on the study of antimalarial activity is the matter of developing a still more convenient host and/or technique for the testing of drugs

With respect to technique the chief questions to be answered are

(1) What is the best method of infecting birds?, by blood inoculation?, by mosquito bite?, or by the use of spontaneously occurring infections?
(2) Which is the proper mode of administering the infection?, by injection?, by stomach tube? or by feeding methods?
(3) When should the drug be given? at the same time as the drug?, a few hours later?, the next day?, or after a longer interval?

Concerning the host used, the present tendency seems to be to choose large birds from which a reasonable amount of blood may be taken for examination without sacrificing the host The question which still remains unanswered, however, is whether malaria can be induced in animals which would be suitable for test work Pl vassali is known to occur in the squirrel and it would seem that this or other varieties of Plasmodia might be used to infect rats or allied animals.

IV <u>Tabular Presentation of Data Relating to Antimalarials of the Type</u>



In the following Tables the headings are, in the main, self-explanatory. However, one or two points which may need some clarification are noted below

(1) Ordinarily the dosages mentioned are given as grams per bird The usual bird weight being about 20 grams

(2) The Identification numbers are those which have been assigned to the respective compounds by the authors who first studied the drugs These numbers may be of assistance in further study of the literature since some clinicians have the unfortunate habit of referring to compounds solely in this way without mentioning the formulae

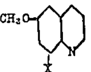
(3) In some cases Fourneau and his Co-Workers give a therapeutic index as a value followed by the symbol ± This follows from the arbitrary way in which this worker chose his test doses i e $\frac{MTD}{4}$, $\frac{MTD}{10}$ A value of 4±, therefore, merely means a therapeutic index which is about 4 and probably less than 4

(4) It will be noted that in the tables the reciprocal of the therapeutic index has been used This value may be used as a direct measure of activity since the true chemotherapeutic index is inversely proportional thereto i e the smaller the fraction the more suitable the compound.

(5) The reference numbers refer to the Bibliography at the end of this section.

Table I

Data Relating to Antimalarials having the Structure



X represents	Ref to Prep	Test Org	Host	Activity	M T D	Ref to Activity	Identification
$-NH_2$	76	Pl relictum Haeroproteus	Canary Sparrow	C I =0 C I =4±	0 0005 0 004	77 78	F-587
$-NHNH_2$	198						
$-CH_3$			Avian	-		119	
$-NHC_4H_9(n)$	5						R-31
$-NHCH_2NH_2$	13		Avian	-		13	
$-NHCH_2N(CH_3)_2$			Sparrow	C I =50		22	
$-NH(CH_2)_2NH_2$	5	Pl relictum	Canary Avian	C I =2 +	0 0006	255 13	R-34
$-NH(CH_2)_2NC_4H_9$		Pl relictum	Canary	C I =2±	0 0006	255	R-35

(contin)

(contin) Table I/ X represents

X represents	Ref to Prep	Test Org	Host	Activity	M T D	Ref to Activity	Identification
$-NH(CH_2)_2N(C_2H_5)_2$		Haemoproteus Pl praecox	Sparrow Siskins	C I =40 C I =6	0 0016	75, 78	F-692 No 7
$-HN(CH_2)_2N(CH_2CH_2CH(CH_3)CH_3)_2$		Haemoproteus	Sparrow	C I =4	0 0008	78	F-718
$-HNCH(OC_2H_5)CH_2NH_2$	6	Pl relictum	Canary	C I =8	0 0006	255	R-48
$-HNCH(OC_2H_5)CH_2NHC_4H_9$		Pl relictum	Canary	C I =1		255	R-49
$-HN(CH_2)_3NH_2$	5, 13, 216	Pl relictum Pl falciparum	Canary Avian Human	C I =16 ++ -	0 0006	255 13, 150 107	R-36
$-HN(CH_2)_3NHC_3H_7(n)$		Pl relictum	Canary	C I =8	0 0003	255	R-52
$-HN(CH_2)_3NHC_3H_7(i)$	6						
$-HN(CH_2)_3NHC_4H_9$		Pl relictum	Canary	C I =8	0 0003	255	R-51
$-HN(CH_2)_3N(CH_3)_2$		Haemoproteus	Sparrow	C I =10	0 001	75	F-574

(contin)

(contin) Table I/ X represents	Ref to Prep	Test Org	Host	Activity	M T D	Ref to Activity	Identification
$-HN(CH_2)_3N(C_2H_5)_2$	154	Haemoproteus Pl praecox	Sparrow Siskins	C I =100 C I =26 6	0 0006	75, 78 137	F-710 No 14 Plasmozid
$-HNCHCH_2N(C_2H_5)_2$ (with CH_3 on CH)	150	Haemoproteus	Sparrow Avian	C I =10 C I = 2	0 0005	75 150, 138	F-776
$-HNCHCH_2N(CH_3)_2$, CH_2–(ring)–OCH_3							
$-HNCHCH_2N(C_2H_5)_2$ (with $CH_2OC_4H_9$ on CH)		Haeroproteus	Sparrow	C I =10	0 0008	78	F-697
$-HN CHCH_2N(C_2H_5)_2$ (with $CH_2OC_2H_5$ on CH)		Haemoproteus	Sparrow	C I =10	0 0006	78	F-703
$-HNCHCH_2N(C_2H_5)_2$ (with CH_2OCH_3 on CH)		Haemoproteus	Sparrow	C I =40±	0 001	78	F-704
$-HNCHCH_2N(C_2H_5)_2$ (with $OCH_2CH(CH_3)_2$)		Haemoproteus	Sparrow	C I ∠4	0 0004	78	F-705
[illegible]		Haemoproteus	Sparrow	C I =10	0 0008	78	F-706

(contin.)

(contin)

Table I/ X represents	Ref to Prep	Test Org	Host	Activity	M T D	Ref to Activity	Identification
$-HNCHCH_2N(C_2H_5)_2$ $CH_2OCH_2CH_2CH(CH_3)_2$		Haemoproteus	Sparrow	C I 4	0 0008	78	F-707
$-HNCHCH_2N(C_2H_5)_2$ $CH_2OC_3H_7(i)$		Haemoproteus	Sparrow	C I =4±	0 0004	78	F-708
$-HNCHCH_2N(CH_3)_2$ $CH_2OCH_2CH_2CH(CH_3)_2$		Haemoproteus	Sparrow	C I =4±	0 0016	78	F-717
$-HNCHCH\ N(CH_3)_2$ $CH_2OCH(CH_3)_2$		Haemoproteus	Sparrow	C I =4±	0 0012	78	F-715
$-HNCHCH_2N(CH_.)_2$ $CH_2OCH_2CH_3$		Haemoproteus	J Sparrow	C L =10±	0 001	78	F-709
$-HNCHCH_2N(CH_3)_2$ CH_2OCH_3		Haemoproteus	J Sparrow	C L =4±	0 0008	78	F-711
$-HNCHCH_2N(CH_3)_2$ $CH_2OCH_2CH_2CH_3$		Haemoproteus	J Sparrow	C I =4±	0 001	78	F-712
$-HNCHCH_2N(CH_3)_2$ $CH_2OCH_2CH(CH_.)_2$		Haemoproteus	J Sparrow	C I -4	0 0008	78	F-713

(contin)

(contin) Table I/ X represents	Ref to Prep	Test Org	Host	Activity	M T D	Ref to Activity	Identification
$-NHCHCH_2N(CH_2)_2$ $CH_2O(CH_2)_3CH_3$		Haemoproteus	J Sparrow	C I =10±	0 0012	78	F-714
$-NH(CH_2)_4NH_2$	75, 216	Pl relictum	Canary Avian	C I =1 +		255 75	R-38
$-NH(CH_2)_4N(C_2H_5)_2$	154	Pl praecox Haemoproteus Haemoproteus	Siskins Sparrow Sparrow	C I =10.6 C I =11 C I =10		127, 154 21 75	No 24 F-765
$-NHCHCH_2CH_2N(C_2H_5)_2$ CH_3		Haemoproteus	Sparrow	C I =10 C I =25	0 00016	78 138	F-736
CH_3 $-NHCH_2-C-N(C_2H_5)_2$ CH_3		Pl praecox	Siskins	C I =2		137	No 27
$-NH(CH_2)_3NH_2$	5, 150	Pl relictum	Canary Avian	± +		255 13	R-38
$-NH(CH_2)_3NHC_4H_9$		Pl relictum	Canary	C I =1±		255	R-39
$-NH(CH_2)_3N(C_2H_5)_2$	154	Pl praecox Haemoproteus	Siskins Sparrow	C I =25 C I =150	0 0004	154 75	F-735
$-NHCH(CH_2)_3N(C_2H_5)_2$ CH_3		Haemoproteus Pl praecox Pl relictum	Sparrow Siskins Canary	C I =150± C I =25 C I =30	0 00016 0 0006	78 137 12, 119	Plasmochin No 30

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Table I/ X represents	Ref to Prep	Test Org	Host	Activity	M T D	Ref to Activity	Identification
$-HNCHCH_2CH_2N(CH_3)_2$ C_2H_5		Haemoproteus	Sparrow	C I =40	0 0008	78	F-695
$-HNCHCH_2CH_2N(C_2H_5)_2$ C_2H_5		Haemoproteus	Sparrow	C I =4	0 00008	78, 75	F-696
$-HNCHCH_2N(C_2H_5)_2$ $C_3H_7(i)$	151	Pl praecox	Siskins	C I =0		137	No 19
CH_3 $-HN-C-CH_2CH_2N(C_2H_5)_2$ CH_3	13						
CH_3 $-HNCH_2CCH_2N(CH_3)_2$ CH_3		Haemoproteus	Sparrow	C I =40	0 0012	78	F-716
CH_3 $-HNCH_2CCH_2N(C_2H_5)_2$ CH_3		Haemoproteus Pl vivax	Sparrow Human	C I =40 +	0 0008	78, 75 190	F-664
$-HN(CH_2)_6N(C_2H_5)_2$	157	Pl praecox Haemoproteus	Siskins Sparrow	C I =13 3 C I =150	0 0006	157, 138 21, 75	F-794
$-HNCH(CH_2)_4N(C_2H_5)_2$ CH_3	151	Pl praecox	Siskins	C I =25		138	

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Table I/ X represents	Ref to Prep	Test Org	Host	Activity	M T D	Ref to Activity	Identification
$-HNCH_2CH_2CHN(C_2H_5)_2$ $C_3H_7(i)$	151	Pl praecox	Siskins	C I =4		137	No 9
$-HNCH_2CHN(C_2H_5)_2$ CH_2 $CH_3-CH-CH_3$		Pl praecox Haemoproteus	Siskins Sparrows	C I =5 3 C I =10±	0 0006	137 78	No 28 F-693
$-HN(CH_2)_7NC_2H_5$	2, 157	Pl praecox Pl relictum Haemoproteus	Siskins Canary Sparrow	C I =33 3 + +		157, 138 2 2, 21	
$-HN(CH_2)_8NH_2$	216						
$-HN(CH_2)_8N(C_2H_5)_2$	2	Pl relictum Haemoproteus	Canary Siskins	+ +		2 2	
$-HN(CH_2)_9N(C_2H_5)_2$	2, 157	Pl relictum Haemoproteus	Canary Sparrow	+ C I =40		? 2, 21	
$-HN(CH_2)_{11}N(C_2H_5)_2$	157	Haemoproteus Pl relictum	Sparrow Canary	C I =3-5 C I =100	0 002(S C)	21 22	F-852
$-HNCH(CH_2)_9N(C_2H_5)_2$ CH_3		Haemoproteus	Sparrow	C I =125		22	F-918

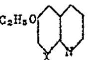
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Table I/ X represents	Ref to Prep.	Test Org	Host	Activity	M T D	Ref to Activity	Identification
$-HN-C(=O)-NH_2$	19	Pl relictum Haemoproteus	Avian Avian	+ -		19 19	
$-HN-C(=O)-NHCH_3$	19	Pl relictum Haemoproteus	Avian Avian	- -		19 19	
$-HNC(=O)NHC_2H_5$	17	Pl relictum Haemoproteus	Avian Avian	- -		19 19	
$-HNC(=O)NHC_3H_7$	17	Pl relictum Haemoproteus	Avian Avian	- -		19 19	
$-HNC(=O)NHC_4H_9(n)$	17	Pl relictum Haemoproteus	Avian Avian	- -		19 19	
$-COOCH_2N(C_2H_5)_2$			Avian	-		5	
$-As(=O)(OH)(ONa)$	76	Pl relictum	Canary Human	± -	0 003-0 005	77 77	F-588
$-COOCH_2CH_2N(C_2H_5)_2$				-		224	
Lupinyl				+			

Table II

Data Relating to Antimalarials having the Structure



X represents	Ref to Prep	Test Org	Host	Activity	M T D	Ref to Activity	Identification
$-NH_2$	76	Haemoproteus Pl relictum	Sparrow Canary Human	C I =<4 C I =0 -	0 0025 0 003-0.005	78 78 78	F-600
$-NHC_4H_9(n)$	5						R-30
$-NH(CH_2)_2NH_2$	181						R-47
$-NH(CH_2)_2N(C_2H_5)_2$		Haemoproteus Pl praecox	Sparrow Siskins	C I =4 C I =4	0 0005	78 137, 154	F-732 No 4
$-N(CH_2)_2N(C_2H_5)_2$ C_2H_5	154	Pl praecox	Siskins	C I =0		137, 154	No 20
$-CHCHN(C_2H_5)_2$ OH C_2H_5	154	Pl praecox	Siskins	C I =0		137	No 22
$-NH(CH_2)_3NH_2$	5	Pl relictum	Canary	C I =16	0 0006	255	R-25

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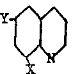
Table II/ X represents	Ref to Prep	Test Org	Host	Activity	M T D	Ref to Activity	Identification
$-HN(CH_2)_3NHC_4H_9$		Pl relictum	Canary	C I =<16		255	R-26
$-HN(CH_2)_3N(C_2H_5)_2$	153	Haemoproteus Pl praecox	Sparrow Siskins	C I =4 C I =13 3	0 00006	75, 78 137, 153, 154	F-730 No. 15
$-HNCH_2CH(OH)CH_2N(C_2H_5)_2$	153	Pl praecox	Siskins	C I =15		153, 154	
$-HNCH(CH_2OC_4H_9)CH_2N(C_2H_5)_2$		Haemoproteus	Sparrow	C I = 4	0 0003	78	F-698
$-HN(CH_2)_3N{<}(CH_2-CH_2)(CH_2-CH_2){>}CH_2$	154	Pl praecox	Siskins	C I =6		137, 154	No 23
$-HN(CH_2)_4NH_2$	181		Avian	C I =30		181	
$-HNCH(CH_3)(CH_2)_3N(C_2H_5)_2$		Pl praecox	Siskins	C I =40		137	No 30
$-HNCH_2CH(CH_3)CH_2N(C_2H_5)_2$		Pl praecox	Siskins	C I =15		137	No 5

(contin.)

(contin) Table II/ X represents	Ref to Prep	Test Org	Host	Activity	M T D	Ref to Activity	Identification
$-NHCH_2C(CH_3)_2CH_2N(CH_3)_2$		Haemoproteus	Sparrow	C I =40	0 0006	78	F-734
$-NHCH_2C(CH_3)_2CH_2N(C_2H_5)_2$		Haemoproteus	Sparrow	C I =10	0 0006	78	F-665
$-NHCH_2CHN(C_2H_5)_2$ $CH_2CH(CH_3)_2$		Haemoproteus	Sparrow	C I =4±	0 0002	77	F-733
$-As=O$ (CH, CH_3)	76	Pl relictum	Canary Human	± -	0 003-0 005	77 77	F-601

Table III

Data Relating to Antimalarials having the Structure



Y represents	X represents	Ref to Prep	Organism	Host	Activity	M T D	Ref to Activity	Identif
$-CH_3$	$-HN(CH_2)_3NH_2$	5						R-21
$-CH_3$	$-CONH(CH_2)_2N(C_2H_5)_2$			Avian	-		244	
-CH	$-HN(CH_2)_{11}N(C_2H_5)_2$				C I =0		22	
-Cl	$-HN(CH_2)_3N(C_2H_5)_2$	150			C I =2 5		150	
-Cl	$-HNCH(CH_3)(CH_2)_2N(C_2H_5)_2$	150						
HO-	$-HN(CH_2)_2N(C_2H_5)_2$	153	Pl praecox	Siskins	C I =13 3		137, 153	No 25
HO-	$-HN(CH_2)_3N(C_2H_5)_2$	150	Haemoproteus Pl praecox	Sparrow Siskins	C I =40 C I =18 5	0 0004	75 150	
HO-	$-HN(CH_2)_{11}N(C_2H_5)_2$				C I =25		22	

(contin)

(contin)
Table III

Y represents	X represents	Ref to Prep	Organism	Host	Activity	M T D	Ref to Activity	Identif
C_3H_7O-(n)	$-HN(CH_2)_3N(C_2H_5)_2$	153	Pl praecox	Siskins	I =1		137, 153	No 11
C_3H_7O-(i)	$-HN(CH_2)_3N(C_2H_5)_2$	153	Pl praecox	Siskins	I =0		137	No 10
C_4H_9O-	$-HN(CH_2)_3N(C_2H_5)_2$	153	Pl praecox	Siskins	C I =1		137, 153	No 12
$C_5H_{11}O$-(i)	$-HN(CH_2)_3N(C_2H_5)_2$	153	Pl praecox	Siskins	C I =0		137	No 6
$C_8H_{17}O$-	$-HN(CH_2)_3N(C_2H_5)_2$	153	Pl praecox	Siskins	C I =0		137, 153	No 8
CH_2=$CHCH_2O$-	$-HN(CH_2)_3N(C_2H_5)_2$	153	Pl praecox	Siskins	C I =0		137, 153	No 26
C_3H_7O-	$-HN\,CH_2C(CH_3)_2CH_2N(C_2H_5)_2$		Haemoproteus	Sparrow	C I =10	0 0006	78	F-694
C_4H_9O-	$-HN(CH_2)_3NH_2$	6	Pl relictum	Canary	C I =8±	0 0003	255	R-44
C_4H_9O-	$-HN(CH_2)_3NHC_4H_9$		Pl relictum	Canary	C I =4		255	R-45

A Plasmochin (Praechine, Beprochen)

1 Origin of Plasmochin

As Schulemann (1932) pointed out, Plasmochin was one of the series of quinoline compounds prepared by the I G Farbenindustrie in their efforts to find an antimalarial which would take the place of the naturally occurring cinchona alkaloids.

The logic followed in arriving at the particular structure which was found to have optimum therapeutic advantages was as follows, according to Schulemann.

It had been known from the work of Ehrlich and Guttmann (1891) that methylene blue I had a specific effect on the malarial parasite and in fact

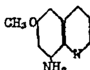


I

this compound had been used fairly frequently, usually as an adjuvant to quinine, to combat malaria since that time (Ziemann 1924)

Following this lead Schulemann, Schonhofer and Wingler (U S P 1,766,403) tried the effect of introducing a dialkylamino alkylene amino group in place of one of the dialkyl amino groups of methylene blue and found that the therapeutic activity was thereby greatly enhanced

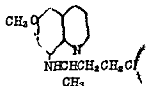
It was on this basis then that steps were taken to determine the effect of adding similar dialkylamino alkylene amino groups to other heterocyclic nuclei and particularly to those which had been demonstrated to have strong specific action against parasites in themselves Such was the case with the quinoline nucleus Early in the work, Schulemann and Mietzsch (U S P 1,747,532) found that 6-methoxy-8-amino quinoline II



II

possessed antimalarial activity and accordingly they proceeded to the preparation of a large number of 6-alkoxy-8-dialkylamino alkylene amino quinolines

The study subsequently led to the synthesis of Plasmochin III



III

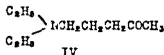
which, it was decided, had the [illegible] relat[illegible] and toxicity of all the quinoli[illegible]

2 Synthesis of Plasmochin

The original synthesis of Plasmochin, as described in Example 3 of U S P 1,747,531, comprised reacting 6-methoxy-8-amino quinoline with α-diethylamino-δ-chloropentane by merely mixing the two reactants and heating at 120-130°C for about 8 hours

The preparation of the 6-methoxy-8-amino quinoline followed the usual methods for obtaining such compounds and will not be elaborated here.

To prepare the dialkylamino isopentyl chloride Schulemann, Schönhofer and Wingler (U S P 1,747,531) reacted diethylamino ethyl chloride with sodio aceto acetic acid ester and then hydrolyzed to obtain the ketone having the formula IV



This ketone was then reduced using sodium amalgam, to the corresponding amino alcohol which was chlorinated in the usual manner with thionyl chloride The product thus obtained was the hydrochloride of diethylamino isopentyl chloride, listed as melting at 93°C

Since the original synthesis was published, others have prepared Plasmochin Compounds by variant methods For example Knunyantz et al (1934) reported on the preparation of a similar compound from 6-methoxy-8-iodo quinoline and 1-amino-5-diethylamino pentane Such methods will be found in the patent literature, however, and space will not be taken to describe them more fully here

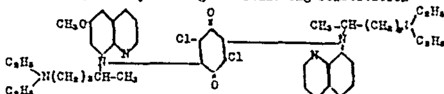
3 Physical Properties and Chemistry of Plasmochin

Plasmochin base is a viscous yellow colored oil which boils at 189-190 C under 2 mm pressure (U S P 1,747,531)

It is sold (Merck Index 1940) as the hydrochloride, a light yellow colored powder which is soluble in about 330 parts of water and freely so in alcohol

The chemistry of the drug was first discussed by Horlein (1926) and Schulemann et al (1932) reported that it has no bitter taste like quinine

According to Andersaag (1938) Plasmochin reacts with chloranil to form a blue dye having the following constitution



which is soluble in organic solvents, imparting thereto a blue color which has been used as the basis for an analytical method for determining the presence of Plasmochin in body fluids A detailed report on the chemical tests for Plasmochin was made by Schulemann, Schönhöfer and Wingler in "Abhandlungen aus dem Gebiete der Auslandskunde, Hamburische University, Vol 26, Series D-Medizin" which may be consulted for further information on this phase of Plasmochin chemistry

4. Toxicity of Plasmochin

In Animals

The toxicity of Plasmochin in animals was studied by Le Heux and Wyngaarden (1929) whose results may be seen from Table (IV)

Table IV

	Plasmochin in mgs per Kg body weight								
	By Mouth			Subcutaneously			Intravenously		
Animal	No Effect	Toxic	Lethal	No Effect	Toxic	Lethal	No Effect	Toxic	Lethal
Rabbit	150	187 5	225	10	15	20	2	3	3.5
Cat	2 5	5	7 5	2 5	3	5-7.5	2 5	2 5	5 0
Dog	-	-	20	-	10	20	-	-	-
Mouse	-	-	-	8 5	10	12 5	-	-	-
Canary	±33	50	50	16.5	25	30-50	-	-	-

Eichholtz (1927) reported that 1 to 2 mgms per Kg given intravenously to cats and rabbits caused a slight fall in blood pressure with rapid recovery, while larger doses of 2 to 3 mgms caused slowing of the heart and cardiac irregularities mainly due to ventricular dysfunction Tskimanauri (1931) on the other hand found that doses of 0 3 mgm per Kg in rabbits caused a short temporary rise in blood pressure and stimulation followed by depression

In general it has been found that the rabbit can destroy Plasmochin much more rapidly than cats and dogs and consequently they respond less with respect to methemoglobin formation, probably due to lesser permeability of the red blood corpuscles (von Oettingen 1933) De Langen and Storm (1934) injected a 0 1% solution of Plasmochin in physiological saline into monkeys and observed a drop in blood pressure and Eichholtz (1935) noted cardiac arrhythemia

In Man

From the clinical use of Plasmochin it has been found that it does not lead to the unpleasant side effects produced by quinine, especially the tinnitus and nausea (Fischl and Schlossberger (1933)) However, the drug is considerably more toxic than quinine (Cordes 1928) Bass (1930) lists the toxic symptoms due to excessive doses of Plasmochin as including cyanosis, pallor, nausea, gastric pain, headaches, vertigo and hemoglobinurea All of these symptoms, he believes, depend upon the hemoglobinurea formation.

Sioli (1926) who was the first to study the antimalarial properties of Plasmochin in paretics found that 0 25 grams daily (0 05 grams 5 times daily) caused marked cyanosis and collapse The dose was reduced by Muhlens (1927) to 0 1 to 0 15 grams daily (0 02 grams 5 times daily or 0 05 grams 3 times daily but he still observed some cyanosis and gastric pains Missiroli and Marino (1934) found that doses as small as 0 02 to 0 06 grams daily, if prolonged for ten days or more produced toxic symptoms in 3 5% of the cases and Cordes (1927) noted intoxication from 0 08 grams per day over a four day period. Likewise, Bastianelli, Mosna and Canalis (1937) reported that 0 02 grams continued for five days produced asthenia, cyanosis, vomiting and gastralgia in nearly 50 per cent of persons

Sinton and Bird (1928) considered that 0 06 grams daily, constituted the safe dosage but at the same time they pointed out that the margin of safety is extremely small.

The League of Nations Report on Malaria (1937) recommends for adults a daily dose of 0 01 grams to 0 03 grams in conjunction with quinine This is also the dosage suggested by the Winthrop Chemical Co , the manufacturers of Plasmochin in the U S A

5 Plasmochin in Avian Malaria

Manwell (1934) presents the relative activity of Plasmochin towards avian parasites in the following order

Pl elongatum
Pl rouxi
Pl relictum
Pl circumflexum
Pl cathemerium

The initial studies on the effect of Plasmochin towards avian malaria were, of course, those of Roehl (1926) who found from his work on Pl relictum infections in canaries, that the drug has a direct action on the plasmodia rather than mobilizing the defense forces of the host His results showed that 1 cc of a 1 50,000 solution of the compound per 20 grams of bird body weight for six days increased the incubation period markedly Hegner and Manwell (1927) confirmed this observation but reported that the drug did not destroy all the parasites Against Pl praecox (syn - Pl relictum) in birds infected by intramuscular injection Manwell (1930) found Plasmochin to be not much better than quinine contrary to opinions held by earlier workers Kritchevskii and Pines (1934) used the drug against Praecox giving 0 02 mgms per gram of body weight over a twelve hour period and stated that the treatment caused the gametocytes of the infecting organism to lose their ability to infect Culex Pipiens The effectiveness of Plasmochin in causing rapid disappearance of blood parasites (Pl praecox) was confirmed by Alexandrescu and Radvan (1937) and Kritchevskii and Rubinstein (1932) observed that whereas Pl praecox tends to gain resistance to quinine, this is not so with Plasmochin

Godoy and Lacorte (1927) studied the effect of Plasmochin on spontaneous Halteridium infections in pigeons and found the drug to be specifically gametocidal with very little effect on the schizonts Similar results were obtained by Collier and Krause (1929) in the rice finch

Against Pl elongatum in canaries infected intramuscularly Manwell (1930) found Plasmochin to be more active than quinine.

Similarly, Manwell (1930) reported Plasmochin to be more active than quinine against Pl cathemerium in canaries This was generally confirmed by Kampler (1930) using 0 1 mgms of drug orally beginning 48 hours after the appearance of parasites in the blood The trophozoites were found to disappear faster than the gametocytes With 0 02 mgms daily Boyd and Dunn (1939) were able to obtain a reduction in the number of merozoites produced per schizont and the period of reproduction was delayed Russell (1931) likewise obtained positive results in the treatment of Pl cathemerium infections with Plasmochin

Lumsden and Bertram (1940) found that 15 mgms per Kg of bird weight was sufficient to prevent subsequent infection of mosquitoes by Pl gallinaceum whereas 2 6 mgms per Kg was inadequate

The above, by no means, constitutes all the available information on the effect of Plasmochin in Avian malaria However, enough has been presented to give a general picture of the situation Additional data will be found in the tabular review of the activity of the 6 - 8 substituted quinolines which precedes this section

Generally speaking, Plasmochin is at least equal to quinine in tertian and quartan malaria but is inferior to quinine in attacking the asexual forms of sub-tertian malaria, (Horlein, 1938) The League of Nations Report on Malaria (1937) summarized the action of Plasmochin as follows

"(1) Action on the trophozoites - The action of plasmochin on the trophozoites of Pl falciparum is almost nil It acts to some extent on the trophozoites of Pl vivax and especially on those of Pl malariae. With small non-toxic doses of plasmochin associated with the usual doses of quinine or atebrin, better results are sometimes obtained on the trophozoites of Pl vivax and even of Pl falciparum

(2) Plasmochin acts upon the gametocytes of the three species, but especially on those of Pl falciparum, which are practically unaffected either by quinine or by atebrin In minimum doses of 0 02 grams, plasmochin devitalises the gametocytes of Pl falciparum, and at the same time diminishes their numbers.

(3) There is no advantage in using plasmochin alone for the treatment of the clinical symptoms of an acute attack in any of the forms of malarial infection

(4) Plasmochin has a definite effect upon the frequency of relapses of benign tertian or quartan In association with quinine or atebrin, or administered after either of these two drugs, it is to a marked degree effective in preventing relapses in benign tertian (except perhaps in the case of a few particular strains) and quartan, and appears similarly to reduce the frequency of malignant tertian relapses "

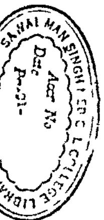
The first studies of the malaricidal action of Plasmochin in man were made by Sioli (1926), Mühlens (1926) and Roehl (1927) The last two workers recognized independently of one another that the drug has a selective action on the gametocytes of malignant tertian malaria

The following table gives briefly a resume of the work of a number of authors who used Plasmochin in the treatment of malaria It should be borne in mind that Plasmochin is today used almost exclusively as an adjuvant to quinine or atebrin since it possesses gametocidal properties only Consequently, after the initial studies clinical workers concentrated on the combinations rather than on Plasmochin alone The data will be presented chronologically

Table V

Malaria Therapy with Plasmochin

Treatment	Type of Malaria	Results	References
0 05 gram twice daily or 0 2 gram five times daily	Tertian Quartan Sub-tertian	Effective Effective Not effective	Muhlens (1926)
0 08 gram daily in two to four doses over 3 days	Induced tertian in paretics Malignant tertian	Effective Fails	Sioli (1926)
	Malaria perniciosa	Plasmochin is not effective	Bärmann and Smits (1927)
0 08 gram daily	------	Eradicated all ring forms on 4th day	Cordes (1927)
0 02 gram three times daily 7 days - 4 days rest - 3 days drug	------	Fever abated 1-2nd day Parasites eliminated on 5th to 6th day	Schulemann & Memmi (1927)
0 06 gram daily	------	Gametes eradicated on 5th day No effect on Schizonts noted	MacPhail (1931)
0 02 gram five times daily or 0 05 gram three times daily	Tropical malaria	Not particularly effective	Muhlens (1927)
0 00125 gram per kilo for 5 - 6 days	All three forms	Freed the peripheral blood of parasites	Sliwensky (1927)
0 01 gram	Tertian	Minimal effective single dose	Fischer (1928)



(continued)

Treatment	Type of Malaria	Results	References
0 06 gram daily	Tertian	Average daily dose required	Fischer (1928)
0 2 gram over 24 - 36 hours	Tropical malaria	Causes crescents to be eradicated	
------	Tertian	Plasmochin is effective against gametes, agametes and schizonts	Lichtenstein (1928)
------	Tropical malaria	Plasmochin is active against agametes	
------	Tropical malaria	Causes rapid degeneration of gametes of tropical malaria	Luyke, Roskoff & Séno (1928)
0 02 gram four to five times daily or 0 05 gram twice daily	Tertian Quartan	Good Results Good Results	Sonak (1931)
0 02 gram per day for three days	Tertian Quartan Aestivo-Autumnal	Effective Effective Not Effective	Sur, Sarkar & Banerzi (1932)

Many other references might be cited in connection with the use of Plasmochin in Malaria Therapy

For example the therapeutic value of Plasmochin against malaria has also been discussed by Hegner and Manwell (1927) who observed that the drug did not destroy all the parasites, S Manoloff-Sliven (1927), Van den Brandon and Herry (1927), Ross (1927), James, Nicol and Shute (1927), Kikuth and Tropp (1927), Manson-Bahr (1927), Stephenson (1927), Whitaker (1927), Zernick (1927), Fischer and Weise (1927), Bhattacharya and Choudhury (1938) who observed no action of Plasmochin on asexual forms of the parasites, Mollow (1928) who argued that Plasmochin caused degeneration of the plasmodia, Muffel (1928), Leiserman (1928)(1930), Barber, Komp and Newman (1929) who observed that plasmochin in small doses of 5 mgms has a definite effect on the viability of Crescents as measured by mosquito infections, Katahira (1929), Whitaker (1929) who confirmed the fact that Plasmochin affects gametes but not schizonts, Whitmore (1929), Hasselmann and Hasselmann-Kahlert (1929), Frizziero (1930), Denowski (1932), Spaar (1933), Jerace (1935), Sobky (1936), Tareev (1936), Kermack (1936), Oesterlin (1937) who suggested that the action of Plasmochin is enhanced by compounds which have an effect on the respiration of cells, Colbert (1938), Marill, Guily and Kessis (1939), Hasselmann (1940), etc

7 Malaria Therapy with Plasmochin - Quinine Combinations

The fact that Plasmochin is satisfactory in tertian and quartan malaria but only partly so in malignant tertian led to the use of Plasmochin and Quinine in conjunction (Nocht and Layer 1937) Since it was found that doses of less than 0 06 gram Plasmochin are sufficient to destroy the crescentic forms and this dose causes toxic reactions in some cases the quinine content was increased and the Plasmochin content reduced

Sinton, Smith and Pottinger (1930) reported cyanosis, gastric pain, vomiting and cramps when 0 06 gram Plasmochin were used in conjunction with 20 grains of Quinine whereas Ronnefeldt (1931) used 0 01 gram Plasmochin with 0 125 gram Quinine over a period of two years and observed no exceptional side reactions In the League of Nations Report on Malaria (1937) a series of experiments is tabulated, on the use of Plasmochin + Quinine giving the percentage of relapses for each type of malaria The dosages used ranged from 0 02 gram Plasmochin + 1 gram Quinine which showed 22 9% relapses in benign tertian malaria, and 3 8% relapses in Malignant Tertian malaria to 0 04 gram Plasmochin and 1 3 grams Quinine which showed about 5% relapses in benign tertian malaria

The terms Quinoplasmin, Chinoplasmin or Plasmochin Compositum have been applied to mixtures of Plasmochin and Quinine

According to Gutman (1941) Chinoplasmin is a combination of 5 mgms Plasmochin with 0 15 gram Quinine Sulfate Nocht and Mayer (1937) list Quinoplasmin as 0 01 gram of Plasmochin plus 0 3 gram Quinine Sulfate or twice the values given by Gutman

The following table indicates the general trend in the use of Plasmochin - Quinine mixtures.

Table VI

Malaria Therapy with Plasmochin + Quinine (Chinoplasmin)

Treatment	Type of Malaria	Results	References
0 06 gram Plasmochin + 0 75 gram quinine for two days	----	Reduced gametocyte count from 26/1000 leucocytes to 8/1000	Barber and Komp (1927)
0 03 gram Plasmochin + 1 2 grams quinine	----	Gave good results	Phelps (1927)
Plasmochin + Quinine	Tropical Malaria	Recommended Rings and Crescents are eradicated	Oliver and Hülstoff (1927)
0 01 g Plasmochin + 0 125 g quinine sulfate	Tertian Aestivo-Autumnal	Blood freed from parasites in 2 - 6 days	Hasselmann-Kahlert (1928)
0 01 gram Plasmochin + 0 1 gram quinine twice daily	Aestivo-Autumnal Sub-tertian	Renders gametocytes non-infectious	Kliegler and Reitler (1929)
0 02 gram Plasmochin + 10 grains quinine twice daily for 21 days	Malignant Tertian	Good results	Mannifold (1931)
0 03 gram + 1 3 grams quinine daily for 21 days	Chronic benign tertian	Optimum treatment	Jarvis (1932)

8 Malaria Therapy with Plasmochin - Atebrin Combinations

Following the discovery that Atebrin was a gametocide like Quinine it was natural that combinations of Plasmochin + Atebrin should be used against malaria

Muhlens (1932) was one of the first to report favorably on the use of Plasmochin and Atebrin against malaria and his results were confirmed by Thounard and Neumann (1932), Komp and Clark (1935), Grayson and Hastings (1936), Manson (1936), Ball (1937), Gentzkow and Callender (1938) and a host of other workers

Manson (1936) claimed that 0 1 gram Atebrin + 0 003 - 0 005 gram Plasmochin in dragees constituted about the best treatment for malaria at that time

The League of Nations Report on Malaria (1937) concludes from experiments made over a period of years that Plasmochin - Atebrin combinations are more toxic than Plasmochin - Quinine Consequently, it was suggested that the two drugs should be administered separately The treatment recommended is 0 3 gram Atebrin daily for five or seven days, followed by 0 02 grams Plasmochin daily for five days The results obtained from such treatment are indicated by a tabular presentation of data showing the percentages of relapses found for the different forms of malaria

9 Prophylactic Value of Plasmochin and Plasmochin Containing Combinations

The question as to whether Plasmochin was capable of acting as a true prophylactic i e hindering the development of invading sporozoites was answered in the affirmative by James, Nicol and Shute (1931) Schaefer (1937) found that daily administration of 0 6 gram of quinine sulfate + 20 mgms of Plasmochin for eight days to each of 1253 Javanese upon their landing at Sumatra resulted in a reduction in the number who subsequently contracted malaria from 30% to 8% Likewise, Baker and Gill (1932) state, as a result of their studies extending over two consecutive years that Plasmochin + Quinine in dosage of 2 tablets weekly (0 01 gram Plasmochin and 0 125 gram quinine sulfate) when administered to all the inhabitants of a district will materially lessen the incidence of malaria

On the other hand, Napier, Butcher and Das Gupta (1932) reported that 10 mgms of Plasmochin given three times per week for three months had no prophylactic action Actually, the incidence of malaria increased and they suggested a possible provocative effect due to small doses of the drug

The League of Nations Fourth General Report of the Malaria Commission (1937) pointed out that

> "We do not possess sufficient data to assess the action of Plasmochin alone, used either therapeutically or prophylactically upon the state of the spleens in malarial communities, for it is nearly always administered together with other drugs"

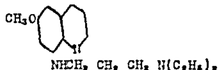
10 Mode of Action of Plasmochin

Very little has been reported concerning the action of Plasmochin on the malarial parasite

Oesterlin (1935)(1936) studied the fluorescence of several varieties of drug and observed that those which were active were strongly fluorescent whereas the inactive compounds were weakly so On this basis he suggested that anti-malarial activity is directly bound up with the emissive characteristics of the drugs How these energy char_cteristics may be related to the energistic set up of the parasite is, however, still a problem for speculation

Berkenheim (1936) discussed an electronic concept of antimalarial action and reasoned that plasmochin must undergo hydrolysis in the organism to give 6-methoxy-8-hydroxy quinoline as the active agent or possibly 6-methoxy-8-amino quinoline which would be less effective.

B Plasmozid (F-710, Rhodoquine, Antimalarin, No 14)



1 Preparation and Properties

Schulemann, Schönhöfer and Wingler claim to have prepared the above compound in 1925 but to have discarded it owing to its high toxicity when compared with Plasmochin Under any circumstances it is broadly covered in D P P 486,079, etc which was filed in 1924

The first disclosure of the compound in the literature appears to be that of Fourneau (1931) who tested its antimalarial activity in birds under the identifying tag F-710 In Russia the drug was reported in a paper by Kritchevskii and Sternberg (1933) under the label No 14, the synthetic details of its preparation being described by Magidson and Strukov (1933) and later by Magidson et al (1936)

Plasmozid Plasmocid or Antimalarin as it has been severally called, is the methylene bis-salicylate of F-710 or No 14 Strukov (1934) first described the preparation of Plasmocid (see also Russ Patent 38,151) as comprising the reaction of 6-methoxy-8-diethyl amino propyl amino oxy quinoline hydrochloride with the ammonium salt of methylene bis-salicylic acid The synthesis was later repeated by Magidson et al (1936) and the technical details involved were elaborated by Vagner (1936)

Originally the term Rhodoquine was used to describe all the quinoline compounds prepared by Fourneau but later it was restricted to include only F-710

With respect to physical properties Plasmocid is described by Tarejev et al (1933) as a yellow brown water insoluble compound F-710 on the other hand is a bright yellow viscous oil which boils at 198-201°C under 1 - 2 mm pressure, and which forms a yellow solid hydrochloride

Dmitriev (1940) tested the reaction of the present compound towards various precipitating agents and reported that both Ehrlich's diazo reagent and the chloranil reaction, which last was assumed to be specific for Plasmochin, are capable of detecting it

2 Toxicity

Sergent et al (1932) made Haemoproteus studies with F-710 and concluded that it was less toxic to birds than Plasmochin

Tarejev (1933) reported that Plasmozid does not produce methaemoglobin Excessive dosages, however, may give rise to epigastric pains, complications in the central and peripheral nervous system and ocular complications, such as partial atrophy of the optic nerve Judging from the number of papers which have appeared in the medical literature concerning ocular complications following the administration of Plasmozid this side reaction would appear to be quite significant Effendiev (1936) recommended that in view of the toxicity of Plasmozid it should be given in doses of 0 06 gram daily instead of 0 15 gram as was the previous practice

Steinberg (1939) studied the toxicity of the compound in cats and gave the lethal dose as 0 02 gram per kilo by mouth Given intravenously the drug causes a fall in blood pressure.

3. Therapeutic Activity

In Avian Malaria

Fourneau (1931) investigated the activity of F-710 in Haemoproteus infections in sparrows and assigned to it a chemotherapeutic index of 150± Kritchevskii and Sternberg (1933) tested it against Pl praecox in siskins and found that under such circumstances the index was 26.6 This activity against Pl praecox was confirmed by Sergent and Vogt (1934) who stated that Plasmozid was active against both gametocytes, and by Kritchevskii and Pines (1934) who stressed the fact that the drug was strongly active against gametocytes

An extremely interesting observation was made by Kritchevskii (1938) and by Kritchevskii and Sternberg (1937) who found that by administering Trypan Blue or Pyrrole Blue to birds having Pl praecox infections at about the same time that somewhat less than the ordinary therapeutic dose of Plasmozid was given the therapeutic index of the last drug increased from 20 to 40 Trypan Blue and Pyrrole Blue in themselves have no antimalarial action

In Human Malaria

Monier (1931) was apparently the first to report favorably on the clinical use of F-710 in human malaria He treated five cases of induced malaria in paretics successfully Marchoux (1931) in the same year found F-710 less toxic and therapeutically more active than plasmochin The following year Sergent, Vogt and Trenz (1932) used the compound to treat twenty cases of sub-tertian and nineteen cases of chronic infection using 0 04 gram on the first day, 0 06 gram on the second day, 0 08 gram on the third and so forth, the treatment lasting from five to nine days The results indicated that the drug had no effect on the schizonts of Pl falciparum and furthermore it was quite toxic Good results were obtained by Decourt (1934) who treated fifty-five cases with 04 - 06 gram per day for 10 days The curative action manifested itself, according to these workers, on doses as small as 0 03 gram per day for three days Sergent and Vogt (1934) stipulated 06 gram as the preferred dose for human treatment.

F-710 has been used in conjunction with Atebrin and with Stovarsol Berny and Nicolas (1936) used 0 02 gram of F-710 together with 0 3 gram of atebrin once a week for six months as a prophylactic and Genevray et al (1939) use 0 005 gram of rhodoquine plus 0 1 gram of quinacrine for the same purpose These last authors obtained very little diminution of the infection rate. Other reports on the use of F-710 and Atebrin include that made by Coulon (1938)

Sautet (1932) and Massias (1933) recommended the use of 0 02 gram F-710 plus 0.25 gram of quinostovarsol four times daily Their course of treatment lasted seven to ten days followed by a week free from drug.

Plasmozid was reported by Tarejev et al (1933) to be useful in daily doses of 0 15 gram (0 05 gram free base) In quartan it worked well with no relapses, and in benign tertian the relapses amounted to about 20% while in malignant tertian it acted like Plasmochin

In conjunction with quinine, Magidson et al (1933) reported 90% cures of tertian and quartan malaria Rashina and Khovanskaya (1939) obtained good results from the use of 0 1 gram of Acrichine three times daily with 0 03 gram of Plasmozid twice daily, on the first and third day These results were confirmed by Platonow (1938).

Sautet (1932) found that Plasmozid, when combined with quinine-acetarsol, was active against all three forms of malaria and Tarejev (1933) reported success in 58 cases of tertian malaria from combined treatment with Plasmozid and Ossarsol

The synergistic action of Pyrrole Blue was noted also in human malaria by Dubrovskaya and Rotenberg (1937) who found that whereas 0 03 gram of Plasmozid taken three to four times daily for two days stopped the attacks in six out of twenty cases and eradicated the plasmodia in two out of ten cases, the intravenous injection of 5 cc of 0 08% Pyrrole Blue at the time of treatment increased the number of attacks stopped to sixteen out of twenty cases and the Plasmodia eradication to twelve out of seventeen cases

3. Therapeutic Activity.

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Sautet (1932) and Massias (1933) recommended the use of 0 02 gram F-710 plus 0.25 gram of quinostovarsol four times daily Their course of treatment lasted seven to ten days followed by a week free from drug

Plasmozid was reported by Tarejev et al (1933) to be useful in daily doses of 0 15 gram (0 05 gram free base) In quartan it worked well with no relapses, and in benign tertian the relapses amounted to about 20% while in malignant tertian it acted like Plasmochin

In conjunction with quinine, Magidson et al (1933) reported 90% cures of tertian and quartan malaria Rashina and Khovanskaya (1939) obtained good results from the use of 0 1 gram of Acrichine three times daily with 0 03 gram of Plasmozid twice daily, on the first and third day These results were confirmed by Platonow (1938).

Sautet (1932) found that Plasmozid, when combined with quinine-acetarsol, was active against all three forms of malaria and Tarejev (1933) reported success in 58 cases of tertian malaria from combined treatment with Plasmozid and Ossarsol

The synergistic action of Pyrrole Blue was noted also in human malaria by Dubrovskaya and Rotenberg (1937) who found that whereas 0 03 gram of Plasmozid taken three to four times daily for two days stopped the attacks in six out of twenty cases and eradicated the plasmodia in two out of ten cases, the intravenous injection of 5 cc of 0 08% Pyrrole Blue at the time of treatment increased the number of attacks stopped to sixteen out of twenty cases and the Plasmodia eradication to twelve out of seventeen cases

C. Cilional (Certuna)

1. Preparation

Cilional or Certuna as it was originally called was introduced in 1938 as a proprietary antimalarial by Bayer, Meister Lucius The constitution of the drug has not been clearly stated in the literature available to date, the closest description being that it is a salt of oxy (dimethyl amino butyl amino) quinoline containing 40 03% of active base (Decourt, Belfort and Schneider (1938))

2. In Vitro Studies

Kikuth (1938) claimed that tests in vitro indicated the activity of Cilional to be about ten times that of Plasmochin

3. In Avian Malaria

Decourt, Belfort and Schneider (1939) summarized the results of their work with Cilional on chickens infected with Pl. gallinaceum by saying that the drug was gametocidal but was less effective, although less toxic, than Plasmochin Kikuth and Mudrow (1939) worked with Pl relictum and Pl cathemerium in birds. They pointed out that Cilional has action on the pigmented blood forms of these parasites but that Plasmochin alone has action on the non-pigmented extra-erythrocytic forms Kikuth (1938) also indicated that the compound attacks the microgametes of Pl cathemerium

4. In Human Malaria.

Chopra and Das Gupta (1938) tested the compound against Pl falciparum infections and claimed that it proved to be about three times as active as Plasmochin Treatment with 0 35 - 0 4 gram daily given in three units of about 0 03 gram was found adequate to eradicate all the gametocytes of this organism from the blood without causing any ill effects to the host This work was fully corroborated by Missiroli and Mosna (1938) who stated that Cilional in conjunction with Quinine or Atebrin would provide a complete remedy against malaria Decourt, Belfort and Schneider (1939) on the other hand reported the drug to be less active than Plasmochin against Pl falciparum

Sioli (1938) tried the drug in doses of 0 07 gram three times daily against tertian malaria and concluded that complete cures could not be obtained This fact, he claimed, served to distinguish Cilional from Plasmochin which does yield cures in tertian malaria

Muhlens (1938) treated cases of tropical malaria with 0 01 - 0 02 gram of Cilional daily in conjunction with Atebrin The gametocytes disappeared from the blood within five days without the slightest apparent side effects being noted

5. Prophylactic Action

Concerning the prophylactic value of Cilional, Sinton et al (1938) reported that, although well tolerated, doses of 0 18 gram daily for seven days failed to prevent infection and therefore concluded that the drug has no true prophylactic action.

D Dimeplasmin

Dimeplasmin is the name given to a product which Green (1929) reported to be of the Plasmochin type and which he used as the salt of a high molecular organic acid, probably 2,2'-dioxy dinaphthyl methane-3,3'-dicarbonic acid (Fischl and Schlossberger 1933)

Very little is known about the compound although Green is reported by Fischl and Schlossberger to have cited experiments by Roehl and Eichholtz which purport to show a therapeutic index equal to that of Plasmochin with less toxicity Sinton, Smith and Pottinger (1930) treated chronic tertian malaria with Dimeplasmin and found it to be very much like Plasmochin

In view of the uncertainty concerning the identity of this compound and the relatively few references to it found in the literature it does not appear to have much significance

E F-852 (F-915, Rhodoquine U or V)

1. Preparation

F-852 was first reported by Fourneau et al (1933) who studied its action in avian malaria Magidson et al (1935) disclosed a method for preparation of the compound two years later

F-915, according to Marchoux and Chorine (1933) is the salt of F-852 with acetylamino hydroxy phenyl arsonic acid.

As indicated under C the term Rhodoquine was formerly applied generally to the quinoline compound prepared by Fourneau, later this term was applied only to F-710

2 Toxicity

Fourneau (1933) incorporated into his original paper some data on the toxic dose for sparrows and rabbits. For the former he gave the value of 0 008 gram per bird by subcutaneous injection, and for the latter, 0 2 - 0 3 gram per kilogram subcutaneously or 0 015 - 0 02 gram per kilogram intravenously Bovet and Demanche (1933) reported the toxic dose for sparrows to be 0 005 gram per 20 gram bird given subcutaneously, for canaries 0 005 gram per bird, for mice 0 008 gram per 20 grams weight subcutaneously and for rabbits 0 4 gram per kilogram subcutaneously or 0 02 gram per kilogram intravenously

In general it was concluded by Eon (1938) who reviewed the subject in his thesis on the action of F-852 and F-915, that F-852 was less toxic than Plasmochin

Sergent and Vogt (1933), however, noted toxic reactions when 0 9 gram of F-915 was given daily to humans

3. In Avian Malaria.

Fourneau found F-852 to have a chemotherapeutic index of 10 against Haemoproteus infections in sparrows, later Bovet and Demanche (1933) reported a value of 3, a figure which was substantially confirmed by Bovet, Benoit and Altman who recorded a ratio of 5 These values may be compared with Plasmochin (C I.= 40) and F-710 (C I = 100) showing F-852 to be less active than either of these other drugs.

Magidson et al (1935) tested the drug against Pl praecox infections in siskins and found that here also the therapeutic index was 5

Bovet, Benoit and Altman (1934) on the other hand found that in canaries F-852 had an index of about 100

4 In Human Malaria

Marchoux and Chorine (1933) tested F-915 in human malaria and found that they could cure the disease in six days using 0 3 - 0 6 gram of drug per day. Sergent and Vogt (1933) likewise found that 0 6 gram of F-915 taken daily caused complete disappearance of all forms of the malarial parasite.

Compounds F-574, 664, and 735

From the many compounds prepared and tested by Fourneau and his Co-workers it was possible to select a number of 6-8 substituted quinolines which possessed high therapeutic activity, low toxicity and stability It should be borne in mind, however, that these selections do not cover all compounds which showed activity Fourneau et al (1933) point out that of forty-eight compounds tested, thirty-eight had activity However, many of these were not stable and underwent changes which produced high toxicity

The selected group of drugs which possess activity combined with low toxicity includes, exclusive of those already discussed, the compounds F-574, F-664, and F-735

Each of these will be considered briefly below

F-574 (Rhodoquine M)

Fourneau et al (1933) give as the structure of F-574 the following



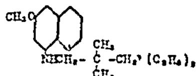
although an earlier paper by Fourneau et al (1930) cites an entirely different structure under the same identifying number However, inasmuch as Lassias (1933) refers to F-574 as the dimethyl analog of F-710, the above structure will be assumed to be the correct one

Fourneau et al (1933) tested the drug against Haemoproteus infections in sparrows and obtained a therapeutic index of about 40

Lassias (1933) found this drug to be less toxic than F-710 and very stable in tropical climates He treated 43 cases of malaria with the compound together with 1 gram quinostovarsol and obtained only two cases of toxic reaction The same worker, Massias (1934), found the drug efficient in benign and malignant tertian malaria but reported that early relapses occurred The daily dosage used by Lassias was 0 08 gram divided into two parts which were given before meals. The treatment extended over 7 - 10 days followed by a drug free week prior to repeated dosage In all cases reported, the parasites were all eradicated before the seventh day

Sicault and Decourt (1934) also studied the clinical use of the compound as did Sautet (1932) who stated that, in his opinion the results obtained with F-574 were much inferior to those resulting from the use of F-710

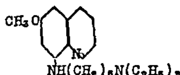
F-664



This preparation was first studied by Fourneau et al (1931) against Haemoproteus infections in sparrows The therapeutic index assigned to the drug was about 40 Lagidson et al (1934) on the other hand report tests carried out against Pl praecox [illegible] note that the index under these conditions is only 2 [illegible] it appears that F-664 has good gametocidal [illegible] power

Monier (1931) undertook clinical tests with this drug against Pl vivax infections He found that daily doses of 0 04 gram were inadequate to remove parasites from the blood Raising the dose to 0 1 gram caused severe toxic symptoms including pallor, weakness, pain in the legs, etc. Good results, however, were obtainable with doses of 0 06 - 0 08 gram daily given intramuscularly as a 1% solution. Total doses of 0.3 gram sufficed to remove all parasites but it was necessary to increase the amount given to 0.5 gram before relapses could be avoided.

F-735



F-735 was reported by Fourneau et al (1933) to have a chemotherapeutic index of 150 against Haemoproteus infections in sparrows, as compared with a value of 40 for both Plasmochin and F-664 Magidson et al (1933) found that the therapeutic index of the same compound against Pl praecox in siskins dropped to 26 Despite the high activity of this compound no obvious references have been found which would indicate that this compound has been used clinically

elationship Between Chemical Structure of 6-8 Substituted Quinolines and heir Therapeutic Activity

It is in this phase of any chemotherapeutic study that the mportance of correlating only the results obtained under comparable onditions, becomes apparent For example indexes obtained by Fourneau t al using Haemoproteus infections in sparrows should not be confused ith the results obtained by those who worked on Pl praecox (relictum) nfections in canaries or siskins The former results demonstrate ;ametocidal activity whereas the latter demonstrate schizonticidal action.

Despite the large amount of data available it has not been ossible to present any arbitrary rules which might be used to govern 'uture synthesis The best that can be done is to demonstrate the effect f certain progressive changes in the chemical structures assuming the onstancy of all remaining groups

Accordingly, it would be undesirable for the reader to ake any of the following statements and to accept it forthwith as applyng generally

In the 6-8 substituted quinoline series, the only group to e discussed here, it is possible to study the effect of (1) Changing the ubstituent in position 6 and (2) Changing the substituent in position 8 ach of these will be taken up under a separate heading

A Effect of Substituents in Position 6

From the results obtained in the extensive te-ts conducted by Fourneau et al (1930)(1931)(1933) it appears that, no matter what the substituent in position 8, the most important group to have in the 6 position is an oxy group Furthermore, the results point to the methoxy group as being most likely to yield optimum activity

In extension of the above conclusions it may be pointed out that

(1) Plasmochin, Plasmozid, etc are 6-methoxy compounds
(2) Replacement of the methoxy group by a methyl group causes a total loss of activity For example

Identification	Position 6	Position 8	M T D	C I
F-710	CH_3O-	-$HN(CH_2)_3NEt_2$	0 0006	100
F-740	CH_3-	-$HN(CH_2)_3NEt_2$	0 0003	0

(3) The methoxy group is not, however, indispensable to antimalarial activity since it may be replaced by H or OH or other alkoxy groups with retention of therapeutic activity This may be exemplified by the following table which utilizes some of Fourneau's results

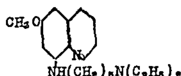
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F-710	CH_3O-	-$HN(CH_2)_3NEt_2$	0 0006	100
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F-772	HO-	-$HN(CH_2)_3NEt_2$	0 0004	40
F-730	C_2H_5O-	-$HN(CH_2)_3NEt_2$	0 0006	4

Kritchevskii and Sternberg (1935) also found that a change from 6-methoxy to 6-ethoxy, 8-diethyl amino ethyl amino quinoline, caused a drop in the index from 6 to 4

It may be noted here that the conclusion that a decrease

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Accordingly, it would be undesirable for the reader to take any of the following statements and to accept it forthwith as applying generally

In the 6-8 substituted quinoline series, the only group to be discussed here, it is possible to study the effect of (1) Changing the substituent in position 6 and (2) Changing the substituent in position 8 Each of these will be taken up under a separate heading

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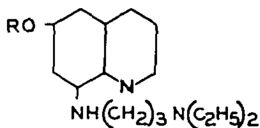
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Kritchevskii and Sternberg (1935) also found that a change from 6-methoxy to 6-ethoxy, 8-diethyl amino ethyl amino quinoline, caused a drop in the index from 6 to 4

It may be noted here that the conclusion that a decrease

EFFECT OF INCREASING THE WEIGHT OF RO- IN



ORGANISM - PL PRAECOX
HOST - SISKINS

THERAPEUTIC INDEX →

7
6
5
4
3
2
1

1 2 3 4 5 6

NO OF CARBON ATOMS IN GROUP RO-

FIG 1

in index occurs when CH_3O is changed to HO (the group in position 8 being $HN(CH_2)_2NEt_2$ is contrary to the finding of Kritchevskii and Sternberg (1933) They reported that a change from CH_3O- to HO in the 6 position (the group in position 8 being $-HN(CH_2)_2NEt_2$) causes an increase in index from 6 to 13 3 Magidson et al (1938), however, were able to confirm the finding of Fourneau et al that a change from CH_3O- to HO- causes a lowering of the therapeutic index.

This disparity clearly shows the danger of concluding too much from too little data

(4) According to Magidson et al (1938) a change of CH_3O to halogen in position 6 has a dystherapeutic effect

(5) With respect to the effect of increasing the weight of the alkoxy group in position 6, the chemotherapeutic index falls as indicated in Fig I which incorporates data presented by Magidson and Strukov (1933) and Kritchevskii et al (1933)(1935)

(6) Introduction of unsaturation into the alkoxy group at position 6 has a dystherapeutic effect according to the data of Kritchevskii and Sternberg (1933) as indicated in the table below

Identification	Position 6	Position 8	C I
No. 10	n-C_3H_7O	$-HN(CH_2)_2N(C_2H_5)_2$	1
No 26	$CH_2=CHCH_2O$	$-HN(CH_2)_2N(C_2H_5)_2$	0

B Effect of Substituents in Position 8

According to D R P 451,730, even simple 6-alkoxy-8-amino quinolines have lethal effect on parasites By and large, however, it appears that the combination Heterocyclic Ring -N-carbon chain-$N\langle^R_R$ appears to be quite significant in connection with antimalarial activity That the efficacy of drugs of this type is not dependent entirely upon the inclusion of any specific ring would seem to be borne out by the fact that such antimalarials have been synthesized in which the ring may be quinoline, acridine, thiazine, etc Accordingly, it appears logical that one must look particularly to the substituents for hints as to the basis for antimalarial activity. In the 6-8 substituted quinolines the diamine grouping in position 8 plays a significant role

In discussing the effect of changes in the diamine group it is expedient to take up, in turn, the various possible ways of varying the chain and the effect of such changes on the therapeutic activity

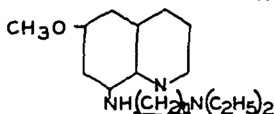
Accordingly, the ensuing discussion will be divided into four parts namely

(1) Effect of Increasing the Length of the Diamine Chain
(2) Effect of Varying the Complexity of the Diamine Chain
(3) Effect of Varying the $-N\langle^R_R$ Group
(4) Effect of Modifying the $\diagdown$R-NH- Group

(1) Effect of Increasing the Length of the Diamine Chain

It was early determined that increasing the length of the diamine chain in the 8 position of a series of homologues of Plasmochin led to a gradual increase in the therapeutic index to a maximum following which the activity declined Furthermore, it was noted that the compounds having chains containing an odd number of carbon atoms showed higher activity than the even numbers

EFFECT OF CHANGING THE WEIGHT OF THE DIALKYLAMINO ALKYL AMINO GROUP IN



THERAPEUTIC INDEX →

150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

?

ORGANISM - HAEMOPROTEUS
HOST - JAVA SPARROW

?

?

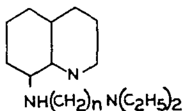
ORGANISM - PL PRAECOX, PL RELICTUM
HOST - SISKINS, CANARIES

2 3 4 5 6 7 8 9 10 11

n →

FIG 2.

EFFECT OF CHANGING THE WEIGHT OF THE DIALKYLAMINO ALKYL AMINO GROUP IN



THERAPEUTIC INDEX →

90
80
70
60
50
40
30
20
10

ORGANISM - HAEMOPROTEUS
HOST - SPARROW

1 2 3 4 5

n →

FIG 3

most closely related thereto This alternation was found to exist by the Russian School including Magidson et al (1933)(1935), Kritchevskii et al (1935) working with Pl praecox in siskins as well as by Bovet et al (1934) and Altman (1935) using Pl relictum in Canaries and Fourneau et al (1933) who worked with *Haemoproteus infections* in Java Sparrows.

In the appended Fig 2 curves are presented which clearly demonstrate the above phenomena As indicated, the lower curve represents the change in therapeutic index as found by working with siskins or canaries, whereas the upper curve gives the results obtained with Java Sparrows.

The difference in the two sets of curves clearly shows that the compounds of the quinoline series have higher gametocidal action than schizonticidal

It will be observed that the maximum in Java Sparrows appears at n= 5 whereas in siskins the maximum is at n= 9. Fourneau (1933) commenting on this relationship expressed the opinion that this difference in maxima supports the view previously held by Bovet (1933) that as the chain was lengthened the gametocidal power of the series recedes and the schizonticidal activity increases.

That the phenomenon discussed above is not restricted to 6-Alkoxy substituted quinolines alone data obtained from Fourneau (1933) is presented in Figure 3. In this case the alkoxy group has been replaced by H but the alternation persists.

(2) Effect of Varying the Complexity of the Diamine Chain.

The variations which have been thus far introduced into the diamine chain include, (a) attachment of side chains at a number of points in the chain, (b) introduction of ether links in the side chain, (c) attachment of hydroxyl groups and (d) introduction of ether links into the chain proper.

(a) Kritchevskii and Sternberg (1933) and Magidson (1934) found that, in general, branching of the carbon chain had a dystherapeutic effect, the index decreasing as the branching approached *proximity to the quinoline nucleus*

Position 6	Position 8	C I.
CH_3O-	$-HNCH_2CH_2N(C_2H_5)_2$	6
CH_3O-	$-NHCH_2CHN(C_2H_5)_2$ with $CH(CH_3)_2$ on the CH	4
CH_3O-	$-NHCHCH_2N(C_2H_5)_2$ with $CH(CH_3)_2$ on the first CH	0

This result was confirmed by Fourneau et al (1931) (1933)

Identification	Position 6	Position 8	C I
F-710	CH_3O-	$-HNCH_2CH_2CH_2N(C_2H_5)$	100
F-664	CH_3O-	$-HNCH_2-C(CH_3)_2-CH_2N(C_2H_5)_2$	40
F-736	CH_3O-	$-HNCHCH_2CH_2N(C_2H_5)_2$ with CH_3 on the first CH	10

From a comparison of the activity of compounds having the chain $-NHCH_2CH_2(CH_2)_nN(C_2H_5)$ with the closely related compounds

in which the first two carbons are arranged in the iso configuration $HNCH(CH_2)_nN(C_2H_5)_2$ it may be concluded that such a change tends to
CH_3 lower the therapeutic index, for example, using Fourneau's data (1933)

Identification	Position 6	Position 8	C I
F-710	CH_3O-	$-HNCH_2CH_2CH_2N(C_2H_5)_2$	100
F-776	CH_3O-	$-HNCHCH_2N(C_2H_5)_2$ CH_3	10
F-7o5	CH_3O-	$-HNCH_2CH_2CH_2CH_2N(C_2H_5)_2$	10
F-736	CH_3O-	$-HNCHCH_2CH_2N(C_2H_5)_2$ CH_3	10
F-735	CH_3O-	$-HNCH_2CH_2CH_2CH_2CH_2N(C_2H_5)_2$	150
Plasmochin	CH_3O-	$-HNCHCH_2CH_2CH_2N(C_2H_5)_2$ CH_3	40

In addition it would aopear that the more complex the side chain, the lower the activity, (Fourneau 1931)

Identification	Position 6	Position 8	C I
F-710	CH_3O-	$-HNCH_2CH_2CH_2N(C_2H_5)_2$	100
F-736	CH_3O-	$-HNCHCH_2CH_2N(C_2H_5)_2$ CH_3	10
F-696	CH_3O-	$-HNCHCH_2CH_2N(C_2H_5)_2$ C_2H_5	4

(b) The addition of ether groups in the side chains is generally unfavorable according to Fourneau (1931) and Henry and Gray (1935) This generalization was made probably because most of the compounds containing such groups have low therapeutic indexes However, if one compares such compounds with the parent from which they may be said to derive the situation does not appear to be so clearly unfavorable

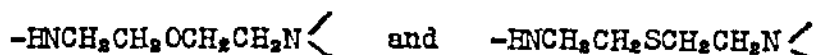
Identification	Position 6	Position 8	C I
F-776	CH_3O-	$-HNCHCH_2N(C_2H_5)_2$ CH_3	10
F-704	CH_3O-	$-HNCHCH_2N(C_2H_5)_2$ CH_2-OCH_3	10
F-703	CH_3O-	$-HNCHCH_2N(C_2H_5)_2$ $CH_2OC_3H_7$	10

As the ether group becomes more complex, it is true that the index decreases

(c) With respect to the effect of introducing hydroxyl groups in the chain, Magidson et al (1933) concluded that the general effect was unfavorable, for example

Position 6	Position 8	C I
CH_3O-	$-HNCH_2CH_2CH_2N(C_2H_5)_2$	26 5
CH_3O-	$-HNCH_2CHCH_2N(C_2H_5)_2$ OH	14

The introduction of oxygen and thio ether links into the diamine chain proper to form compounds containing the grouping



$$-HNCH_2CH_2OCH_2CH_2N< \quad \text{and} \quad -HNCH_2CH_2SCH_2CH_2N<$$

is disclosed by Schulemann (1932) as having constituted a phase of the work carried on at the I G Farbenindustrie Laboratories There does not appear to be any data available, however, from which one might check the specific effect of such changes on anti-malarial activity If one may judge from the fact that none of these compounds has passed beyond the stage of laboratory investigation that they have no worthwhile activity, then our conclusion must be that such changes have a dystherapeutic effect.

(3) Effect of Varying the $-N\langle^R_R$ Group

The changes which have been thus far effected in the $-N\langle^R_R$ group comprise (a) Increasing the weight of the alkyl groups R (b) Making the R groups part of an heterocyclic substituent (c) Replacing one or both of the R groups by H

According to the results obtained by Fourneau (1931) (1933) the replacement of $-N\langle^{CH_3}_{CH_3}$ by $-N\langle^{C_2H_5}_{C_2H_5}$ makes very little difference in the therapeutic index.

Identification	Position 6	Position 8	C I.
F-574	CH_3O-	$-HNCH_2CH_2CH_2N(CH_3)_2$	100
F-710	CH_3O-	$-HNCH_2CH_2CH_2N(C_2H_5)_2$	100

Replacement of the $-N\langle^R_R$ group by $-N\langle^{CH_2-CH_2}_{CH_2-CH_2}\rangle CH_2$, however, has a dystherapeutic effect according to the results of Kritchevskii and Sternberg (1933)

Identification	Position 6	Position 8	C I
No. 15	C_2H_5O-	$-HNCH_2CH_2CH_2N(C_2H_5)_2$	13 3
No. 23	C_2H_5O-	$-HNCH_2CH_2CH_2N\langle^{CH_2-CH_2}_{CH_2-CH_2}\rangle CH_2$	6

For the effect of replacing the R groups by hydrogens, reference may be made to the work of Tate and Vincent (1933), who found that 6-methoxy-8,γ-amino propyl amino quinoline (R 36) had an index of 16 when tested by Roehl's method Likewise, 6-methoxy-8,γ-butyl amino propyl amino quinoline had an index of 8

As indicated above it is somewhat hazardous to make comparisons between the results obtained by two different authors unless the techniques used may be accepted as comparable Tate and Vincent (1933) used Pl relictum in canaries while Kritchevskii and Sternberg (1933) used the same organisms (Syn Pl praecox) in siskins Accordingly, although the following comparison may be valid the results should only be assumed as qualitative at the most.

Comparing the results of Tate and Vincent (1933) with the value 26.6 which Kritchevskii et al (1933) obtained for 6-methoxy-8-diethyl amino propyl amino quinoline one might conclude that replacement of one or both alkyl groups by hydrogen causes a reduction in therapeutic activity.

(4) Effect of Changing the -NH- Group

Magidson et al (1933) replaced the H in the -NH- group of a series of malarials by the $-C_2H_5$ group and concluded from their results that the change had a dystherapeutic effect

VII Tabular Presentation of Data Relating to Quinoline Antimalarials Having Substituents in Positions Other Than 6,8

The Tables have been arranged in the following order

Mono-substituted quinolines having groups attached in the 2, 4, 5, 6 and 8 positions

Di-substituted quinolines having groups attached in the 1, 6, 2, 3, 2, 4, 2, 6, 4, 6, 5, 6, 5, 8, and 7, 8 positions

Tri-substituted quinolines having groups attached in the 2, 4, 6, 2, 4, 8, 3, 6, 8 and 5, 6, 8 positions

Tetra-substituted quinolines having groups attached in the 2, 3, 4, 6 and 2, 4, 6, 7 positions

Table VII

Data Relating to Antimalarials Having the Structure

Y represents	Ref to Prep	Test Org	Host	Activity	Ref to Activity	Identif
-OH		Pl Cathemerium	Canary	-	97	
-CH(CO)(CO)C₆H₄	-	Pl relictum	Canary	-	73	
 OH	212					
-NH-C₆H₄-SO_2NH_2	18					
N(H)(-C_2H_5)(-C_2H_5)(Cl)	76	Pl relictum	Canary	C I =0	77	F-566

(contin)

(contin)
Table VII

X represents	Ref to Prep	Test Org	Host	Activity	Ref to Activity	Identif
$-NHCH_2CH_2NH_2$	76	Pl relictum	Canary	C I =0	77	F-564
$-NHCH_2-]_2$	76	Pl relictum	Canary	C I =0	77	F-565
$-N\langle(CH_2-CH_2)(CH_2-CH_2)\rangle CH_2$	76	Pl relictum	Canary	C I =0	77	F-583
$-N\langle(CH_2-CH_2)(CH_2-CH_2)\rangle NCH_2C(CH_3)_2-OH$	76	Pl relictum	Canary	C I =0	77	F-584
$-CH_2CH_2N(C_2H_5)_2$	-114					
$-CH_2CH_2N\langle(CH_2-CH_2)(CH_2-CH_2)\rangle CH_2$	114					
$-CH(CH_3)-CH_2N\langle(CH_2-CH_2)(CH_2-CH_2)\rangle CH_2$	114					

(contin)

(contin)

Table VII

X represents	Ref to Prep	Test Org	Host	Activity	Ref to Activity	Identif
$-CH=CH-C_6H_4-NH(CH_2)_3NH_2$	179					

(contin)

Table VII

X represents	Ref to Prep	Test Org	Host	Activity	Ref to Activity	Identif
$-NHCH_2CH_2NH_2$	76	Pl relictum	Canary	C I =0	77	F-564
$-NHCH_2-]_2$	76	Pl relictum	Canary	C I =0	77	F-565
$-N<(CH_2-CH_2)(CH_2-CH_2)>CH_2$	76	Pl relictum	Canary	C I =0	77	F-583
$-N<(CH_2-CH_2)(CH_2-CH_2)>NCH_2C(CH_3)_2-OH$	76	Pl relictum	Canary	C I =0	77	F-584
$-CH_2CH_2N(C_2H_5)_2$	-114					
$-CH_2CH_2N<(CH_2-CH_2)(CH_2-CH_2)>CH_2$	114					
$-CH(CH_3)-CH_2N<(CH_2-CH_2)(CH_2-CH_2)>CH_2$	114					

(contin)

(contin)
Table VII

X represents	Ref to Prep	Test Org	Host	Activity	Ref to Activity	Identif
$-CH=CH-$$NH(CH_2)_2NH_2$	179					

(contin)
Table VII

X represents	Ref to Prep	Test Org	Fost	Activity	Ref to Activity	Identif
$-NHCH_2CH_2NH_2$	76	Pl relictum	Canary	C I =0	77	F-564
$-NHCH_2-]_2$	76	Pl relictum	Canary	C I =0	77	F-565
$-N\langle(CH_2-CH_2)(CH_2-CH_2)\rangle CH_2$	76	Pl relictum	Canary	C I =0	77	F-583
$-N\langle(CH_2-CH_2)(CH_2-CH_2)\rangle NCH_2C(CH_3)_2-OH$	76	Pl relictum	Canary	C I =0	77	F-584
$-CH_2CH_2N(C_2H_5)_2$	-114					
$-CH_2CH_2N\langle(CH_2-CH_2)(CH_2-CH_2)\rangle CH_2$	114					
$-CH(CH_3)-CH_2N\langle(CH_2-CH_2)(CH_2-CH_2)\rangle CH_2$	114					

(contin)

(contin)

Table VII

X represents	Ref to Prep	Test Org	Host	Activity	Ref to Activity	Identif
-CH=CH  $NH(CH_2)_3NH_2$	179					

(contin / Table VII

X represents	Ref to Prep	Test Org	Host	Activity	Ref to Activity	Identif
$-NHCH_2CH_2NH_2$	76	Pl relictum	Canary	C I =0	77	F-564
$-NHCH_2-]_2$	76	Pl relictum	Canary	C I =0	77	F-565
$-N\langle{}^{CH_2-CH_2}_{CH_2-CH_2}\rangle CH_2$	76	Pl relictum	Canary	C I =0	77	F-583
$-N\langle{}^{CH_2-CH_2}_{CH_2-CH_2}\rangle NCH_2C(CH_3)_2-OH$	76	Pl relictum	Canary	C I =0	77	F-584
$-CH_2CH_2N\langle{}^{C_2H_5}_{C_2H_5}$	-114					
$-CH_2CH_2N\langle{}^{CH_2-CH_2}_{CH_2-CH_2}\rangle CH_2$	114					
$-CH(CH_3)-CH_2N\langle{}^{CH_2-CH_2}_{CH_2-CH_2}\rangle CH_2$	114					

(contin)

(contin)
Table VII

X represents	Ref to Prep	Test Org	Host	Activity	Ref to Activity	Identif
 $-CH{=}CH-C_6H_4-NH(CH_2)_3NH_2$	179					

(contin)
Table VII

X represents	Ref to Prep	Test Org	Host	Activity	Ref to Activity	Identif
$-NHCH_2CH_2NH_2$	76	Pl relictum	Canary	C I =0	77	F-564
$-NHCH_2-]_2$	76	Pl relictum	Canary	C I =0	77	F-565
$-N\langle^{CH_2-CH_2}_{CH_2-CH_2}\rangle CH_2$	76	Pl relictum	Canary	C I =0	77	F-583
$-N\langle^{CH_2-CH_2}_{CH_2-CH_2}\rangle NCH_2C(CH_3)_2-OH$	76	Pl relictum	Canary	C I =0	77	F-584
$-CH_2CH_2N\langle^{C_2H_5}_{C_2H_5}$	-114					
$-CH_2CH_2N\langle^{CH_2-CH_2}_{CH_2-CH_2}\rangle CH_2$	114					
$-CH(CH_3)-CH_2N\langle^{CH_2-CH_2}_{CH_2-CH_2}\rangle CH_2$	114					

(contin)

[illegible] Having the Structure



represents	Ref to Prep	Test Org	Host	Activity	Ref to Activity	Identif
$\frown NH_2$	18					
$-CH_2R$	115					

Table VIII

Data Relating to Antimalarials Having the Structure



X represents	Ref to Prep	Test Org	Host	Activity	Ref to Activity	Identif
-NH-C_6H_4-SO_2NH_2	18					

Table IX

Data Relating to Antimalarials Having the Structure



X represents	Ref to Prep	Test Org	Host	Activity	Ref to Activity	Identif
-HNSO₂-C₆H₄-NH₂ ($-HNSO_2C_6H_4NH_2$)	18					
$-CH_2R$	115					

Table X

Data Relating to Antimalarials having the Structure



X represents	Ref to Prep.	Test Org	Host	Activity	Ref to Activity	Identif
$-CH_2R$	115					
$-OH$		Pl Cathemerium	Canary	-	97	
$-OC_3H_7$		Pl Cathemerium	Canary	-	97	
$-CH_2N\langle CH_2-CH_2 / CH_2-CH_2 \rangle CH_2$	115					
$-CH_2CH_2N(C_2H_5)_2$				-	224	

(contin)

Table XI

Data Relating to Antimalarials Having the Structure



X represents	Ref to Prep	Test Org	Host	Activity	Ref to Activity	dentif
$-HN(CH_2)_3NH_2$	234					R-41
$-HN-CH(C_2H_5)(CH_3)$	27					
$-HN(CH_2)_2NH_2$	27					
$-HNSO_2C_6H_4NH_2$	18					
$-CH_2-N(CH_2-CH_2)_2CH_2$	115					
$-HN(CH_2)_2N(C_2H_5)_2$		Pl praecox Haemoproteus	Siskins Sparrow	C I =0 C I =0	137 75, 78	 F-731

(contin)
Table XI

X represents	Ref to Prep	Test Org	Host	Activity	Ref to Activity	Identif
HO-		Pl Cathemerium	Canary	-	97	Quinasol as salt with Potassium Bisulfate.
C_3H_7O-		Pl Cathemerium	Canary	-	97	
C_4H_9O-		Pl Cathemerium	Canary	-	97	
$-HN(CH_2)_3N(C_2H_5)_2$		Haemoproteus	Sparrow	C I =80	75, 78	F-728
$-HN(CH_2)_5N(C_2H_5)_2$		Haemoproteus	Sparrow	C I =40	75	F-747
$-CH_2OH$			Avian	-	119	
$-CH_2-C_6H_4-NH_2$	115					
$-CH_2-N(C_2H_5)_2$	115					

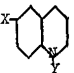
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Table XI

X represents	Ref to Prep	Test Org	Host	Activity	Ref to Activity	Identif
$-CH_2-N(CH_2-CH_2)(CH_2-CH_2)N-CH_2-$ (quinoline ring, N)			Avian	-	119	
$-CH_2-NHCH_2CH_2N(C_2H_5)_2$			Avian	-	119	
$-NH-CH(CH_3)-(CH_2)_3-N(C_2H_5)_2$	278					

Table XII

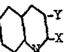
Data Relating to Antimalarials Having the Structure



X represents	Y represents	Ref to Prep	Test Org	Host	Activity	Ref to Activity	Identification
HO-	$-(CH_2)_2NH_2$	234					R-13
HO-	$(CH_2)_2NH_2$ -< Cl	234					R-9
CH_3O-	$-(CH_2)_2NH_2$	234					R-10
CH_3O-	$(CH_2)_2NH_2$ -< Cl	234					R-12
CH_3O-	$(CH_2)_3NH_2$ -< Cl	234					R-6

Table XIII

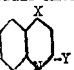
Data Relating to Antimalarials Having the Structure



X represents	Y represents	Ref to Prep	Test Org	Host	Activity	Ref to Activity	Identification
$-CH_3$	$-CH\ CH_2N(C_2H_5)_2$				-	114	
$-CH_3$	$-COCH_2N<(CH_2-CH_2, CH_2-CH_2)>CH_2$				-	114	
$-(CH_2)_2-N(C_2H_5)$-cyclohexyl	$-C_2H_5$	224					

Table XIV

Data Relating to Antimalarials Having the Structure



X represents	Y represents	Ref to Prep	Test Org	Host	Activity	Ref to Activity	Identification
$-C(C_2H_5)_3$	-⬡	76	Pl relictum	Canary	C I =0	77	F-519
$-COOC_2H_5$	-⬡-NH_2	76	Pl relictum	Canary	C I =0	77	F-520
$-COOH$	-⬡-NH_2	76	Pl relictum	Canary	C I =0	77	
$-COOC_2H_5$	-⬡-OH	76	Pl relictum	Canary	C I =0	77	F-521
$-COOC_2H_5$	$-CH_3$		Pl relictum	Canary	C I =0	77	F-522
$-CONH_2$	-⬡		Pl relictum	Canary	C I =0	77	
$-COOC_2H_5$	$-CH_2CH(CH_3)_2$		Pl relictum	Canary	C I =0	77	

(contin)

(contin)
Table XIV

X represents	Y represents	Ref to Prep	Test Org	Host	Activity	Ref to Activity	Identification
-COOH	OH ⬡		Pl relictum	Canary	C I =0	77	
$-COOC_2H_5$	OH ⬡		Pl relictum	Canary	C I =0	77	
$-COOCH_3$	-⬡		Pl relictum	Canary	C I =0	77	F-508
$-CH_3$	-O-⬡	197					
-O-⬡	$-CH_3$	197					
$-CH_3$	-O-⬡-CH, NO_2	197					
$-NHCOCH_3$	-⬡		Pl, praecox	Canary	+	111	
-NH⬡$N(CH_3)_2$	-⬡		Pl praecox	Canary	-	111	
$-N\langle CH_2-CH_2, CH_2-CH_2 \rangle NH$	$-CH_3$	116					Km -13

(contin)

(contin)
Table XIV

X represents	Y represents	Ref to Prep	Test Org	Host	Activity	Ref to Activity	Identification
$-N\langle{}^{CH_2-CH_2}_{CH_2-CH_2}\rangle N-$	$-CH_3$	116					Km -14
$-N\langle{}^{CH_2-CH_2}_{CH_2-CH_2}\rangle CH_2$	$-CH_3$	116					Km -10

Table XV

Data Relating to Antimalarials Having the Structure



X represents	Y represents	Ref to Prep	Test Org	Host	Activity	Ref to Activity	Identification
-Cl	$-N(C_2H_5)C_2H_5$ (with Cl, H)	76	Pl relictum	Canary	C I =0	77	F-567
CH_3O-	$-N(C_2H_5)C_2H_5$ (with Cl, H)	76	Pl relictum	Canary	C I =0	77	F-568
CH_3O-	$-HN-CH(CH_3)(CH_2)_3N(C_2H_5)_2$	152			-	152	
CH_3O-	$-HN(CH_2)_4N(C_2H_5)_2$	152			-	152	
CH_3O-	$-HNCH_2CH(OH)CH_2N(C_2H_5)_2$	152			-	152	

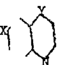
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Table XV

X represents	Y represents	Ref to Prep	Test Org	Host	Activity	Ref to Activity	Identification
CH_3O-	$-CH=CH-CH=CH$ NH_2	179					
CH_3O-	$-CH=CH$ $-NH(CH_2)_3NH_2$	179					
CH_3O-	$-$ $-NH(CH_2)_3NH_2$	179					
CH_3-	C_6H_5-	161					
CH_3O-	$-$ $-NH(CH_2)_3NH_2$	179					

Table XVI

Data Relating to Antimalarials Having the Structure



X represents	Y represents	Ref to Prep	Test Org	Host	Activity	Ref to Activity	Identification
CH_3O-	$HNCH(CH_2)_3N(C_2H_5)_2$ (with CH_3 on CH)	152	Pl relictum	Siskins	+ +	152 276	
CH_3O-	$HN(CH_2)_4N(C_2H_5)_2$	152	Pl relictum	Siskins	+ +	152 276	
CH_3O-	$HNCH_2-CHCH_2N(C_2H_5)_2$ (with OH on CH)		Pl relictum	Siskins	+ +	152 276	
CH_3O-	CH–C–CH_3 ‖ ‖ –C N \ / N C_6H_5	147					
CH_3O-	$-HNCH(CH_2)_2N(C_2H_5)_2$ (with CH_3 on CH)		Pl relictum	Siskins	+	276	

(contin)
Table XVI

X represents	Y represents	Ref to Prep	Test Org	Host	Activity	Ref to Activity	Identification
CH_3O-	$-CHOHCH_2N(C_2H_5)_2$	275	Pl relictum	Canary	-	275	
CH_3O-	$-CHOHCH_2N(C_4H_9)_2$	275	Pl relictum	Canary	+	275	
CH_3O-	$-CHOHCH_2N(C_5H_{11})_2$	275	Pl relictum	Canary	+	275	
CH_3O-	$-CHOHCH_2N(C_5H_{11})_2$(i)	275	Pl relictum	Canary	-	275	
CH_3O-	$-CHOHCH_2N(C_6H_{13})_2$	275	Pl relictum	Canary	+	275	
CH_3O-	$-CHOHCH_2N(C_7H_{15})_2$	275	Pl relictum	Canary	-	275	
CH_3O-	$-CHOHCH_2N$ $\langle$ CH_2-CH_2 / CH_2-CH_2 $\rangle$ CH_2	275	Pl relictum	Canary	-	275	
CH_3O-	$-CHOHCH_2-N$ $\langle$ CH_2-CH_2 / CH_2-CH_2 $\rangle$ CH – N $\langle$ CH_2-CH_2 / CH_2-CH_2 $\rangle$ CH_2	275	Pl relictum	Canary	-	275	

(contin)

(contin)
Table XVI

X represents	Y represents	Ref to Prep	Test Org	Hc	vity	Ref to Activity	Identification
CH_3O-	$-NH-C(=O)-NH-$		Pl praecox	Canary	-	111	
CH_3O-	$-COCH=C(-CH_3)-NH-$ (CH, CH_2-CH, $C-CH_3$, CH_2-CH_2 ring)	147					
CH_3O-	$-COOCH_2CH_2N(C_2H_5)_2$				-	224	
CH_3-	$-COCH_2CH_2CH_2N(C_2H_5)_2$				-	224	
CH_3O-	$-CH_2NH(CH_2)_2N(C_2H_5)$				-	281	

Table XVII

Data Relating to Antimalarials Having the Structure



X represents	Y represents	Ref to Prep	Test Org	Host	Activity	Ref to Activity	Identification
$-NO_2$	$-N<(CH_2-CH_2, CH_2-CH_2)>CH_2$	119		Avian	-	119	
$-HN(CH_2)_2NH_2$	$-NH_2$	76	Pl relictum	Canary	C I =0	77	F-582
$-NH_2$	$-HN(CH_2)_2NH_2$	76	Pl relictum	Canary	C I =0	77	F-576
$-HN(CH_2)_2NH_2$	$-NO_2$	76	Pl relictum	Canary	C I =0	77	F-573
$-NO_2$	$-HN(CH_2)_2NH_2$	76	Pl relictum	Canary	C I =0	77	F-570
$-NO_2$	$-HN(CH_2)_3N(C_2H_5)_2$		Haemoproteus	Sparrow	C I =0	75	F-774

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(contin)
Table XVII

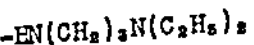
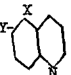
X represents	Y represents	Ref to Prep	Test Org	Host	Activity	Ref to Activity	Identification
 $-NH_2$	$-HN(CH_2)_3N(C_2H_5)_2$		Haemoproteus	Sparrow	C I =10	75	F-775

Table XVIII

Data Relating to Antimalarials Having the Structure



X represents	Y represents	Ref to Prep	Test Org	Host	Activity	Ref to Activity	Identification
$-NO_2$	$-HN(CH_2)_2NH_2$ HCl		Pl relictum	Canary	C I =0	77	F-571
$-NH_2$	$-HN(CH_2)_2NH_2HCl$		Pl relictum	Canary	C I =0	77	F-574
$-NH_2$	$-OC_2H_5$		Pl Cathemerium	Canary	-	97	
$-COOCH_2CH_2N(C_2H_5)_2$	$-OCH_3$				-	224	

Table XIX

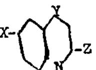
Data Relating to Antimalarials Having the Structure



X represents	Y represents	Ref to Prep	Test Org	Host	Activity	Ref to Activity	Identification
$-HN(CH_2)_2NH_2$	$-NO_2$	76	Pl relictum	Canary	C I =0	77	F-572
$-HN(CH_2)_2NH_2$	$-NH_2$	76	Pl relictum	Canary	C I =0	77	F-575
$-As(=O)(OH)(ONa)$	$-NO_2$	76	Pl relictur	Canary	C I =0	77	F-596

Table XX

Data Relating to Antimalarials Having the Structure



X represents	Y represents	Z represents	Ref to Prep	Test Org	Host	Activity	Ref to Activity	Identif
CH_3-	$-COOC_2H_5$	$-C_6H_5$	76	Pl relictum	Canary	C I =0	77	F-516
CH_3-	$-C(C_2H_5)_3$	$-C_6H_5$	76	Pl relictum	Canary	C I =0	77	F-517
CH_3O	$-COOC_2H_5$	$-C_6H_5$	76	Pl relictum	Canary	C I =0	77	F-518
CH_3O	-COOH	$-C_6H_4-NH_2$		Pl relictum	Canary	C I =0	77	
CH_3O	$-NHC_2H_5$	$-C_6H_5$			Avian	-	73	
CH_3O-	$-NHCH_3$	$-C_6H_5$			Avian	-	73	

(contin)

(contin)
Table XX

X represents	Y represents	Z represents	Ref to Prep	Test Org	Host	Activity	Ref to Activity	Identif
CH_3O-	$-N(CH_3)_2$	$-C_6H_5$			Avian	-	73	
CH_3O-	$-N(C_2H_5)_2$	$-C_6H_5$			Avian	-	73	
CH_3O-	$-NHCH=CH_2$	$-C_6H_5$			Avian	-	73	
CH_3O-	-NH⟨cyclohexane ring⟩N(CH)₂	$-C_6H_5$			Avian	-	73	
CH_3O-	$-NH_2$	$-C_6H_5$		Pl praecox	Canary Avian	- -	111 73	
CH_3O-	$-CH_3$	$-C_6H_5$			Avian	-	73	
CH_3O-	$-N\langle{}^{CH_2-CH_2}_{CH_2-CH_2}\rangle N-COCH_2Cl$	$-CH_3$	117					
CH_3O-	$-N\langle{}^{CH_2-CH_2}_{CH_2-CH_2}\rangle NH$	$-CH_3$	116					Km -9

(contin)

Table XX

X represents	Y represents	Z represents	Ref to Prep	Test Org	Host	Activity	Ref to Activity	Identif
CH_3O-	$N{<}^{CH_2-CH_2}_{CH_2-CH_2}{>}N-COCH_3$	$-CH_3$	116					Km -11
CH_3O-	$N{<}^{CH_2-CH_2}_{CH_2-CH_2}{>}N-$	$-CH_3$	116					Km -15
CH_3O-	$HN(CH_2)_2N{<}^{CH_2-CH_2}_{CH_2-CH_2}{>}CH_2$	$-CH_3$	117			-	117	
CH_3O-	$HN(CH_2)_2N{<}^{CH_2-CH_2}_{CH_2-CH_2}{>}N$	$-CH_3$	117					
CH_3O-	$-N{<}^{CH_2-CH_2}_{CH_2-CH_2}{>}CH_2$	$-CH_3$	116					Km -12
CH_3O-	HN-(cyclohexane ring)-$N(C_2H_5)_2$	$-C_6H_5$			Avian	-	73	
CH_3O-	$-CH_3$	$-OH$	191					

(contin)

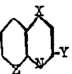
(contin)

Table XX

X represents	Y represents	Z represents	Ref to Prep	Test Org	Host	Activity	Ref to Activity	Identif
CH_3O-	HN–(ring)–As=O (OH, OH)	$-CH_3$	241					
CH_3O-	HN–(ring)–(ring)–As=O (HO–, OH)	$-CH_3$	241					
CH_2O-	–HN–(ring)–CH_2–(ring)–NH–	$-CH_3$	241					
C_2H_5O-	$-CH_3$	$-CH_3$		Pl cathemerium	Canary	–	97	
C_2H_5O-	$-NH_2$	$-C_6H_5$		Pl praecox	Canary	+	111	
CH_3O-	$-O(CH_2)_3NH_2$	$-CH_3$	216					

Table XXI

Data Relating to Antimalarials Having the Structure



X represents	Y represents	Z represents	Ref to Prep	Test Org	Host	Activity	Ref to Activity	Identif
CH_3-	-CH	CH_3O-	191					

Table XXII

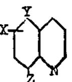
Data Relating to Antimalarials Having the Structure



X represents	Y represents	Z represents	Ref to Prep	Test Org	Host	Activity	Ref to Activity	Identification
CH_3-	NO_2	Br			Avian	-	119	

Table XXIII

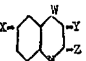
Data Relating to Antimalarials Having the Structure



X represents	Y represents	Z represents	Ref to Prep	Test Org	Host	Activity	Ref to Activity	Identif
$-OCH_3$	$-HNCOCH_3$	$-HNC_4H_9$	5					
$-OCH_3$	-Br	$-CH_3$	119		Avian	-	119	
$-OCH_3$	$-HN(CH_2)_2NH_2$	$-NO_2$	76	Pl relictum	Canary	C I =0	77	F-593
$-OCH_3$	$-NO_2$	$-NH(CH_2)_3N(C_2H_5)_2$		Haemoproteus	Sparrow	C I =0	75	F-782
$-OCH_3$	$-NH_2$	$-HN(CH_2)_3N(C_2H_5)_2$		Haemoproteus	Sparrow	C I =0	75	F-783
$-OCH_3$	-Cl	$-NH(CH_2)_3NH_2$	216					

Table XXIV

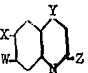
Data Relating to Antimalarials Having the Structure



X represents	W represents	Y represents	Z represents	Ref to Prep	Host	Test Org	Activity	Ref to Activity	Identif
CH_3O-	-CH(OH)- (H, OH)	-H	-OH				+	73	

Table XXV

Data Relating to Antimalarials Having the Structure



X represents	Y represents	W represents	Z represents	Ref to Prep	Test Org	Host	Activity	Ref to Activity	Identif
CH_3O-	$HN(CH_3)_2$	CH_3O	CH_3	185					

VIII *Relationship Between Antimalarial Activity and Chemical Constitution in Quinoline Compounds other than the 6-8 Substituted Derivatives*

A check through the tables reveals that very few compounds which have substituents in positions other than 6-8 are active against malaria

The exceptions to this are

(1) Compounds F-728 and F-747 which have the groups $-NH(CH_2)_3N(C_2H_5)_2$ and $-NH(CH_2)_5N(C_2H_5)_2$ respectively in the 8 position and no other substituent The fact that the RO- grouping in the 6 position may be replaced by H- with retention of antimalarial activity has been mentioned previously

(2) Several compounds in which the 6 position retains the RO-grouping but in which the dialkyl amino alkylene amino group has been shifted from the 8 to the 4 position are reported to have activity
In this connection it should be observed that according to Galperin (1940) the compounds 4-(diethylamino isopentyl) amino 6-methoxy quinoline, 4-(diethylamino butyl) amino 6-methoxy quinoline, 4-(diethylamino isobutyl) amino 6-methoxy quinoline and 4-(diethylamino oxy propyl) amino 6-methoxy quinoline all have a strong schizonticidal action on infections of Pl relictum in the siskin This is quite the reverse of the situation in the corresponding 6-8 substituted quinolines which all have strong gametocidal action

IX Antimalarial Compositions (exclusive of the 6-8 Substituted Types) which have been Studied Clinically

A Paludex

Paludex, according to Niven (1938) is a preparation of the Union Chimique Belge It comprises a combination of 0 2 grams of a double salt of Oxy quinoline disulfonic acid with sodium and copper plus 0.1 gram quinine hydrochloride The product is obtainable in the form of green tablets which are soluble in water

Clinically the drug has been used to combat malaria, and particularly Pl falciparum malaria, by Van Nitsen (1936)(1937) and Van Nitsen and Serra (1936) These workers administered doses of 1 gram on the first day and increased the amount by 0 2 gram each day until the sixth day By this treatment both the schizonts and gametocytes of all species of parasites were claimed to be eliminated

Niven (1938) on the other hand, used the composition on 29 cases of Pl falciparum malaria giving 1 5 gram doses and reported that the drug had no action on the gametes and was definitely less active than quinine In addition, Kingsbury (1938) reported that Paludex did not control the parasites or fever of Pl falciparum malaria, and Rodhain and Hendrix (1937) were unable to detect any favorable action in bird malaria against Pl cathemerium, or Halteridia infections In monkeys the drug failed to cure Pl knowlesi and Pl gonderi infections

Obviously the activity of this compound is in considerable doubt and much additional work would be necessary to obtain a fair evaluation

B Plasmodex

Chopra (1938) reports that Plasmodex is similar to Paludex except for a higher percentage of copper.

C. Preparations R-118 and R-123

According to Sternberg (1934) R-118 and R-123 are modifications of the same compound, the constitution of which is apparently not available beyond the fact that it is a quinoline derivative

Reports on the drugs have been published by Collier and Co-Workers (1929)(1931) These reports indicate that the compound has prophylactic action against avian malaria in canaries and is successful in the treatment of tertian and quartan malaria

The above authors claimed a chemotherapeutic index of 250 for the compound against Pl praecox infections in canaries, thus indicating an activity about 8 times that of Plasmochin

Sternberg (1934), however, tested the drug in siskins (Acanthus Linaria) and obtained a value of 26 6 for R-118(123) as compared with 40 for Plasmochin

From these data it would appear that either the value of 250 was a mistake or else a remarkably active compound was found This latter situation seems unlikely, however, in view of the lack of interest which has since been shown in the drug.

X. Quinoline Antimalarials which Possess Complex Structure

A number of antimalarial preparations have been reported in which the quinoline ring forms part of a more complex ring structure In most cases however, the work seems to have stopped at the synthesis, no pharmacological data being available

General Structure	Antimalarial Activity	References
Pyridoquinolines (structure: R_2, $-R_1$, N)	No report	Kermack & Weatherhead (1940)
Glyoxalinoquinolines (structure: N, C, N)	+(Paramoecia)	Narang and Ray (1
Pyrroloquinolines (structure: NH, -R, N)	No report	Robinson (1929)
Benziminazolyl-quinolines (structure: CH_3, NH, C, N, CH_3, N)	No report	Ghosh (1937) Ghosh (1938)
Phenanthridines (structure: CH_3O, N, $-N(CH_2)_nN(C_2H_5)_2$)	No report	Walls (1935)

(contin)

General Structure	Antimalarial Activity	References
Furanoquinolines CH_3O, CH_3O, CH, C–R, N, O	No report	Haq, Kapur and Ray (1933)
Quinazolines N, N, N, CH_2NHCO	No report	Ghosh (1937)
Pyrazoloquinolines OH, C–CH_3, N, N, N	No report	Ghosh (1937)
Chromanequinolines CH_2, O, N	Too insoluble for test as antimalarials	Das Gupta and Bhattacharjee (1931)

XI. Toxicity of Quinoline Compounds Towards Paramoecia

As has been pointed out previously the use of toxicity determinations against Paramoecia as a criterion of antimalarial activity is of doubtful validity

Accordingly it is not planned to include in this review a survey of the large number of such determinations which have been made with compounds of the quinoline series Such information has been collected in reviews such as those published by Houben (1939), von Oettingen (1933) etc and recourse may be had to such volumes if the subject should be of further interest to the reader

Reference may be made at this time, however, to the studies made by Brahmachari and his Co-workers in India partly because the work is relatively recent and also because of the type of compound studied In one of the earlier papers (1930) a statement is included that "antipro-ozoic" compounds were to be sought and it is likely that malaria was the protozoan disease which they had in mind

In the table below is given the name of the compound studied, the activity towards paramoecia where available and the years in which the pertinent papers were published The activity is represented by the usual + for active, ± somewhat active and - for inactive

Name of Compound	Activity	Reference Brahmachari & Co-Worke
2-methyl-4-phenyl-8-amino quinoline	+	(1930)(1931)
2-methyl-4-phenyl-8-nitro quinoline		(1930)
2-methyl-4-phenyl-6-nitro quinoline		(1930)
2-methyl-4-phenyl-6-amino quinoline	-	(1930)
2-p-dimethyl amino styryl-6-oxy quinoline	-	(1930)
2-p-dimethyl amino styryl-6-methoxy quinoline		(1930)
2-p-dimethyl amino styryl-6-ethoxy quinoline	-	(1930)
2-p-dimethyl amino styryl-4-phenyl-8-nitro quinoline		(1930)
2-methyl quinoline-6-amino acetyl-p-arsanilic acid		(1931)
2-methyl-6-methoxy-8,β-dimethyl amino isopropyl amino quinoline 2 HCl		(1932)
2-p-dimethyl amino styryl quinoline HCl		(1931)
2-p-dimethyl amino styryl-6-methyl quinoline CH_3I	-	(1931)
2-methyl-6-chloro-8-amino isopropyl amino quinoline HCl	±	(1931)
6-amino quinoline	+	(1930)
6-oxy-8-amino quinoline	+	(1931)
6-methoxy-5-amino acetyl-p-arsanilic acid		(1931)
6-carbamido quinoline		(1931)
6-amino quinoline-N-methylene sulfinate Na salt		(1931)

(contin

(contin)

Name of Compound	Activity	Reference
		Brahmachari & Co-Workers
6-methoxy-8-amino quinoline		(1931)
6-methoxy quinoline-8-amino acetamide	-	(1930)
6-methoxy-8,β-dimethyl amino isopropyl amino quinoline 2 HCl		(1932)
6-methoxy-8,β-amino isopropyl amino quinoline		(1931)
6-methoxy-8-amino quinoline-N-methylene sulfinate Na salt		(1931)
6-amino quinoline-p-arsanilate	-	(1931)
6-methoxy-8-carbamido quinoline		(1931)
6-methoxy-8,β-amino isopropyl amino quinoline	±	(1932)
6-methoxy-8,β-methyl amino isopropyl quinoline		(1932)
6-ethoxy-8,n-lactyl amino quinoline		(1932)
6-ethoxy-β-hydroxy propyl-8-amino quinoline		(1932)
6-ethoxy-8,β-amino isopropyl amino quinoline		(1932)
6-ethoxy-8-allyl thiocarbamido quinoline		(1932)
6-ethoxy-8-allyl amino quinoline		(1932)
6-methyl-8,β-amino isopropyl amino quinoline		(1931)
6-methyl-8,β-dimethyl amino isopropyl amino quinoline 2 HCl		(1932)
6-oxy quinoline-8-glycine amine	+	(1931)
Quinoline-6-amino acetamide	+	(1930)
6-oxy quinoline-8-amino acetamide	+	(1930)
6-chloro-8-amino isopropyl amino quinoline 2 HCl	+	(1930)
8-amino ethyl amino quinoline HCl	+	(1930)
8-amino quinoline	-	(1930)
Quinoline-8-amino acetamide	-	(1930)
8-amino quinoline-N-methylene sulfonate		(1931)
8-carbamido quinoline		(1931)
8-n-lactyl amino quinoline HCl		(1932)
8-allyl amino quinoline		(1931)
8-allyl thiocarbamido quinoline		(1931)
8,β-amino isopropyl amino quinoline	+	(1931)
β-hydroxy propyl-8-amino quinoline HCl		(1932)
8-amino quinoline-p-arsanilate	±	(1931)
8,β-dimethyl amino isopropyl amino quinoline 2 HCl		(1932)

XII Patent Literature

U S Patents

German Patents

British Patents

Canadian Patents

French Patents

Indian Patents

Russian Patents

(contin)

Name of Compound	Activity	Reference
		Brahmachari & Co-Workers
6-methoxy-8-amino quinoline		(1931)
6-methoxy quinoline-8-amino acetamide	-	(1930)
6-methoxy-8,β-dimethyl amino isopropyl amino quinoline 2 HCl		(1932)
6-methoxy-8,β-amino isopropyl amino quinoline		(1931)
6-methoxy-8-amino quinoline-N-methylene sulfinate Na salt		(1931)
6-amino quinoline-p-arsanilate	-	(1931)
6-methoxy-8-carbamido quinoline		(1931)
6-methoxy-8,β-amino isopropyl amino quinoline	±	(1932)
6-methoxy-8,β-methyl amino isopropyl quinoline		(1932)
6-ethoxy-8,n-lactyl amino quinoline		(1932)
6-ethoxy-β-hydroxy propyl-8-amino quinoline		(1932)
6-ethoxy-8,β-amino isopropyl amino quinoline		(1932)
6-ethoxy-8-allyl thiocarbamido quinoline		(1932)
6-ethoxy-8-allyl amino quinoline		(1932)
6-methyl-8,β-amino isopropyl amino quinoline		(1931)
6-methyl-8,β-dimethyl amino isopropyl amino quinoline 2.HCl		(1932)
6-oxy quinoline-8-glycine amine	+	(1931)
Quinoline-6-amino acetamide	+	(1930)
6-oxy quinoline-8-amino acetamide	+	(1930)
6-chloro-8-amino isopropyl amino quinoline 2 HCl	+	(1930)
8-amino ethyl amino quinoline HCl	+	(1930)
8-amino quinoline	-	(1930)
Quinoline-8-amino acetamide	-	(1930)
8-amino quinoline-N-methylene sulfonate		(1931)
8-carbamido quinoline		(1931)
8-n-lactyl amino quinoline HCl		(1932)
8-allyl amino quinoline		(1931)
8-allyl thiocarbamido quinoline		(1931)
8,β-amino isopropyl amino quinoline	+	(1931)
β-hydroxy propyl-8-amino quinoline HCl		(1932)
8-amino quinoline-p-arsanilate	±	(1931)
8,β-dimethyl amino isopropyl amino quinoline 2 HCl		(1932)

XII Patent Literature

U S Patents

German Patents

British Patents

Canadian Patents

French Patents

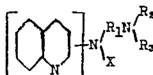
Indian Patents

Russian Patents

U S P 1,728,189 — Schulemann, Mietzsch and Schönhöfer
Assigned to Winthrop Chemical Co , Inc
Corresponds to D R P 492,250 (See)
B P 310,559
S P. 136,379
138,594

U S P. 1,747,531
Feb 18, 1930 — Schulemann, Schönhöfer and Wingler
Assigned to Winthrop Chemical Co , Inc.
Corresponds to D R P. 486,079
B P 267,169
S P 127,178

Claims compounds of the general formula

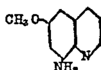


wherein X may be H, alkyl, amino alkyl or other monovalent substituent R_1 may be an alkylene residue in which the hydrogen atoms may be replaced by monovalent substituents such as the hydroxyl group R_2 and R_3 represent H, alkyl, amino alkyl groups and the quinoline nucleus may be further substituted.

A number of examples are given Plasmochin is claimed specifically in Claim 7

U S.P 1,747,532
Feb. 18, 1930 — Schulemann, Schönhöfer and Wingler
Assigned to Winthrop Chemical Co , Inc
Corresponds to D R P 451,730

Discloses and claims



as a strong specific agent against blood parasites

U S.P. 1,758,378
May 13, 1930 — Schulemann, Schönhöfer and Wingler
Assigned to Winthrop Chemical Co , Inc.
Corresponds to D R P. 490,188
B P. 307,727
S.P. 132,307

Preparation of 6-alkoxy-8-amino quinolines by subjecting 6-alkoxy quinoline-8-carboxylic acid amides to the Hoffmann reaction.

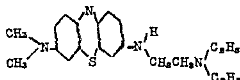
U S P 1,760,781
May 27, 1930

Schulemann, Schönhöfer and Wingler
Assigned to Winthrop Chemical Co , Inc
Corresponds to D R P 490,275 (See)
B P 282,453
S P 134,218

U S P. 1,766,403
June 24, 1930

Schulemann, Mietzsch and Wingler
Assigned to Winthrop Chemical Co , Inc
Corresponds to D R P. 488,945

This patent discloses derivatives of the methylene blu type wherein one of the $-N\langle^{CH_3}_{CH_3}$ groups is replaced by dialky amino alkylene amino chains As an example of the type of compound covered



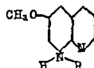
U S P 1,879,538
Sept 27, 1932

Schönhöfer
Assigned to Winthrop Chemical Co , Inc
Corresponds to D R P 531,083 (See)
B P 351,068
S P 154,173

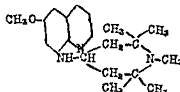
U S P 1,903,196
Mar 28, 1933

Schulemann, Schönhöfer and Wingler
Assigned to Winthrop Chemical Co , Inc.

Discloses and claims compounds of the general formula



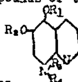
wherein R represents an hydroaromatic radical which is substituted by secondary or tertiary amino groups The specific type of compound covered may be exemplified by



U S P 1,938,047
Dec 5, 1933

Schönhöfer and Andersaag
Assigned to Winthrop Chemical Co , Inc.

Discloses compounds of the general structure

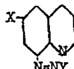


wherein R_1 and R_2 represent alkyl groups, R_3 represents a basic radical containing nitrogen as a primary, secondary or tertiary amine R_4 represents H, an alkyl group or a basic radical containing nitrogen as a primary, secondary or tertiary amine.

U S P 1,972,988
Sept. 11, 1933

Giemsa, Oesterlin and Pützer
Assigned to Winthrop Chemical Co , Inc
Corresponds to D R P. 551,094
B P. 399,818

Covers compounds of the general structure

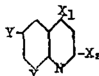


wherein X represents H or an alkoxy group and Y represent the radical of hydrocupreine

U.S P. 2,034,983
Mar. 24, 1936

Jensch
Assigned to Winthrop Chemical Co , Inc.

Covers products of the general structure



wherein X_1 represents H, amino or alkyl amino, X_2 represen H, methyl, amino or alkyl amino, at least one X being amir or alkyl amino and Y represents the group $-N\langle^{Z_1}_{Z_2}$ in which Z represents H or acyl and Z_2 represents H or alkyl.

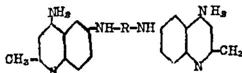
P 2,050,971
. 11, 1936

Jensch
Assigned to Winthrop Chemical Co , Inc.
Corresponds to D R P 639,243 (See)

U S P 2,092,352
Sept. 7, 1937

Jensch
Assigned to Winthrop Chemical Co , Inc.
Corresponds to D R P 606,497

Compounds of the type

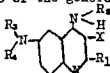


where R is a cyanuric acid radical, as anti-protozoal agen

U S P. 2,066,730
Jan 5, 1937

Jensch
Assigned to Winthrop Chemical Co Inc

Compounds of the general formula



where X= nitro or amino
R_1= methyl or H
R_2= alkyl or H
R_3= Acyl or H
R_4= alkyl or H

Particular reference to 6-acyl amino-3,4-diamino quinolines as specifics against blood parasites

U S P 2,086,691
July 13, 1937

Zerweck and Kunze
Assigned to General Aniline Works, Inc
Corresponds to D R P 615,184 (See)

D R P 55,119
1890

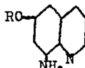
Einhorn

Discloses the preparation of 2,4-dioxy-3,4-dihydro-6-methoxy quinoline for use against malaria

D R P 451,730
Oct. 13, 1927

Schulemann, Mietzsch and Schönhöfer
Assigned to I G Farbenindustrie
Corresponds to U S P 1,747,532

Discloses compounds of the general structure



wherein R may be CH_3, C_2H_5, as compounds having strong specific action against blood parasites

D R P 468,809
Nov 8, 1928

J D Riedel E de Haën, Akt Ges.

Discloses 2-phenyl quinoline 4-carboxylic acid, cadmium salt as an antimalarial

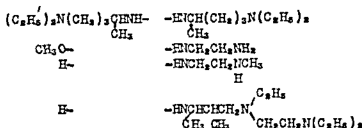
D R P 486,079
Oct 31, 1929

Schulemann, Schönhöfer and Wingler
Assigned to I G Farbenindustrie
Corresponds to U S P 1,747,531
B P 267,169
S P 127,178 (Addition to S P 125,832)

Preparation of N-substituted amino quinolines as agents for use against blood parasites Includes specific disclosures of the following compounds in examples

Position 6	Position 8
H-	$-HNCH_2CH_2N(C_2H_5)_2$
H-	$-HNCHCHCH_2N(CH_3)_2$ CH_3 CH_3
CH_3O-	$-HNCHCH_2CH_2CH_2N(C_2H_5)_2$ CH_3
CH_3O- NH_2(Posit 1)	$-HNCHCH_2CH_2CH_2N(C_2H_5)_2$ CH_3
CH_3O-	$-HNCH_2CHCH_2N(C_2H_5)_2$ OH
C_2H_5O-	$-HNCHCHCH_2N(CH_3)_2$ CH_3 CH_3
CH_3O-	$-HNCH_2CH_2OCH_2CH_2N(C_2H_5)_2$
CH_3O-	$-HNCH_2CH_2$-S-$CH_2CH_2N(C_2H_5)_2$
CH_3O-	$-HNCH_2CHCHCH_2N(CH_3)_2$ OH CH_3
CH_3O-	$-HNCHCH_2CH_2CH_2N(CH_3)_2$ CH_3

(continued)



D R P 488,945
Dec 19, 1929

Schulemann, Wingler and Mietzsch
Assigned to I G Farbenindustrie
Addition to D R P 486,079 Earlier addition D R P 486,771

Discloses thiazines and oxazines of the methylene blue type in which one of the dialkyl amino groups is replaced by a dialkyl amino alkyl amino group

D R P 490,188
Jan 9, 1930

Schulemann, Mietzsch and Wingler
Assigned to I G Farbenindustrie
Addition to D R P 451,730
Corresponds to U S P 1,758,378
B P 307,727 (Addition to B P 267,457)
S P 132,307 (Additions S P 134,828-29)

Discloses the preparation of 6-alkoxy-8-amino quinolines via the Hofmann Degradation

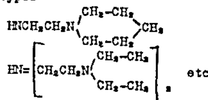
D R P 490,275
Jan 9, 1930

Schulemann, Schonhöfer and Wingler
Assigned to I G Farbenindustrie
Addition to D R P 486,079 Refers to earlier additions D R P 486,771, 488,890, 488,892, 488,945
Corresponds to U S P 1,760,781
B P 282,453
S P 134,018 (Addition to S P 136,292)

Discloses an additional series of N-substituted amino quinolines having action against blood parasites

Also discloses a methylene blue derivative wherein one of the $N(CH_3)_2$ groups is replaced by $-N\langle^{CH_3}_{CH_2CH_2N\langle^{CH_2-CH_2}_{CH_2-CH_2}\rangle CH_2}$

The quinoline substituents include groups in the 8 position of the types



D R P 492,250
Feb 6, 1930

Schulemann Mietzsch and Schönhöfer
Assigned to I G Farbenindustrie
Addition to D R P 451,730
Corresponds to U S P 1,728,189
B P 310,559 (Addition to

S P 136,379
138,594

Discloses the preparation of 6-alkoxy-8-amino quinolines from 6-alkoxy quinoline 8-carbonic acid alkyl esters by means of the Curtius degradation

D R P 531,083
July 23, 1931

Schönhöfer
Assigned to I G Farbenindustrie
Corresponds to U S P. 1,879,538
B P 351,068
S P 154,173 (Addition 154,829)

Describes the preparation of 5,6-Dialkoxy-8-amino quinoline

D R P 551,094
May 4, 1932

Giemsa, Oesterlin and Pützer
Assigned to I G Farbenindustrie
Corresponds to B P. 399,818
U S P 1,972,988 (See)

Method for preparation of quinoline-8-azo compounds of the quinine series Quinoline-8-azo hydrocuprein, etc
For use against malaria

D R P 536,447
Oct 8, 1931

Schönhöfer and Andersaag
Assigned to I G. Farbenindustrie
Corresponds to B P 354,352
S P 154,658 (Additions 160,092-95)

Discloses the preparation of N-substituted 5,6-Dialkoxy-8-amino quinolines Substituents of the dialkyl amino alkylene amino type suggesting that the compounds were contemplated as antimalarials although such use is not mentioned in the specification

D R P. 602,049
Aug. 30, 1934

Rothmann and Fricker
Assigned to I G Farbenindustrie
Corresponds to B P 433,625

Preparation of 6,8-substituted quinolines by condensation of 6-chlor or 6-methoxy-8-amino quinoline with β-diethyl amino ethanol or γ-diethyl amino propanol

D R P 606,497
Dec 4, 1934

Jensch
Assigned to I G Farbenindustrie
Corresponds to F P 414,105
U S P 2,092,352

Method for preparation of cyanuric compounds containing diamino quinoline nuclei
Useful against protozoal diseases
For details see U S P 2,092,352

D R P 615,184
June 28, 1935

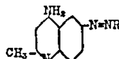
Zerweck and Kunze
Assigned to I G Farbenindustrie
Corresponds to U S P. 2,080,691
B P 437,317
S P 183,198 (Additions 185,831, 188,766, 188,767 and 188,765)

Method of preparing amino compounds of the quinoline series substituted in the 2 or 4 positions by dialkyl amino alkylene amino group.

D R P 622,596
Dec 2, 1935

Jensch
Assigned to I G Farbenindustrie

Method for preparation of azo compounds of the quinoline series for use against blood parasites
Compounds have the general structure

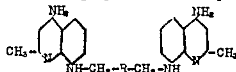


wherein R may be a benzene, quinoline, pyrazolone, etc nucleus

D R P 639,243
Dec 1, 1936

Jensch
Assigned to I G Farbenindustrie
Corresponds to U S P 2,050,971
B P 459,131
S P 186,669, 191,460, 192,996
Aust P 153,814

Discloses the preparation of compounds of the type



wherein R= CH_2, CHOH, etc

D R P 650,491
Sept 23, 1937

I G Farbenindustrie
Addition to D R P 602,049

Preparation of N-amino alkyl derivatives of cyclic amino compounds by condensing the latter with aliphatic amino alcohols in presence of an alkaline condensing agent

D R P 678,150
July 11, 1939

Kikuth
Assigned to I G Farbenindustrie
Corresponds to B P 498,752
S P. 129,425

Preparation of 6-hydroxy-8-amino quinolines in which the N atom of the 8-amino group is connected by a chain of

three carbon atoms to a N atom of an aliphatic or cyclo aliphatic amine or of a saturated heterocyclic compound

British Patents

B P 267,169
Sept 7, 1925

I G Farbenindustrie
Corresponds to U S P 1,747,531
D R P 486,079
S P 127,178

B P 267,457
Mar 7, 1927

I G Farbenindustrie

Preparation of 6-methoxy-8-nitro quinoline and 6-ethoxy-8-nitro quinoline by Skraup's reaction
Compounds are active against blood parasites.

B P 275,277
Aug 4, 1927

I G Farbenindustrie

Preparation of 6-alkoxy-8-amino quinolines by reducing the 8-nitro or 8-azo derivative of 6-alkoxy quinoline
Compounds for use against blood parasites

B P 282,453
Mar 19, 1929

I G Farbenindustrie
Addition to B P 267,169
Corresponds to U S P. 1,760,781
D R P 490,275
S P 134,218

B P 307,727
Mar 12, 1929

I G Farbenindustrie
Addition to B P 267,457
Corresponds to U S P 1,758,378
D R P 490,188
S P 132,307

B P 310,559
Apr 29, 1929

I G Farbenindustrie
Addition to B P 267,457
Corresponds to U S P 1,728,189
D R P 492,250
S P 136,379
138,594

B P 321,974
Nov 21, 1929

I G Farbenindustrie

Process for preparing quinoline compounds containing aliphatic amino substituted side chains by condensing an aliphatic amino alkyl aldehyde or ketone or an N-alkyl substitution product thereof with o-amino benzaldehyde or an o-amino phenyl ketone or an homologue of either

B P 351,068
Mar 22, 1930

I G Farbenindustrie
Corresponds to U S P 1,879,538
D R P 531,083
S P 154,173

B P 354,352 Aug 4, 1931	I G Farbenindustrie Corresponds to D R P 536,447 S P. 154,658
B P 399,818 Oct 11, 1933	I G Farbenindustrie Corresponds to U S P. 1,972,988 D R P 551,094
B P 433,625 Feb 17, 1934	I G Farbenindustrie Corresponds to D R P. 602,049
B P 437,317 Oct 28, 1935	I G Farbenindustrie Corresponds to U S P. 2,086,691 D R P 615,184 S P. 183,198
B P. 459,131 Dec 28, 1936	I G Farbenindustrie Corresponds to U S P 2,050,971 D R P 639,243 S P 186,669 Aust P 153,814
B P 498,752 Jan 9, 1939	I G Farbenindustrie Corresponds to S P 129,425 D R P. 678,150
B.P 504,024 Apr 13, 1939	Altman Corresponds to Dutch P 42,540 Fr. P 832,542

Procedure of reducing a mixture of straight chain ω,ω'-dicarboxylic acids having 7 to 12 carbon atoms, to the corresponding diol Treating the product with hydrogen halide to form halo-hydroxy alkyl compounds Causing these to react with a dialkyl amine, replacing the OH of the product with halogen and reacting with an amine substituted or heterocyclic compound The products are of the type- 6-methoxy-8(ω-diethyl amino octyl or nonyl amino) quinolines

Can P 271,590
June 14, 1927

Canadian Patents

Schulemann, Schönhöfer and Wingler

Relates to polyamino quinoline derivatives and intermediate products for their manufacture consisting of the respective amino derivative being made strongly basic by the introduction of N atoms which are combined with the aromatic amino groups through the medium of aliphatic radicals

Fr P 769,263 1934 — Soc des Usines Chimiques Rhone-Poulenc

The ethyl ester of 11 bromo undecylenic acid is heated in the presence of diethyl amine and the diethyl amino undecylate reduced by sodium in alcohol to form diethyl amino undecylenic alcohol This compound subjected to the action of thionyl chloride is reacted with thionyl chloride to give the corresponding chloride which may be reacted with 6-methoxy-8-amino quinoline.

Indian Patents

Ind P. 25,810
1939

I G Farbenindustrie

Process comprising introducing a basic radical into the amino group of 4-amino quinolines which contain at least a further substituent in the seven position by the action of reactive esters of basic alcohols or condensation with the basic alcohols themselves

Russ P 38,151 1934

Strukov

Covers the reaction of an aqueous solution of 6-methoxy-8-diethyl amino propyl amino, oxy quinoline hydrochloride with an aqueous solution of the ammonium salt of methylene bis salicylic acid. The precipitate which formed was filtered off and dried for use as an antimalarial

The product thus obtained is Plasmozid

Russ P 44,553 1935

Magidson and Madajewa

Used the reaction product of 6-methoxy-8-amino quinoline with salts of diethyl 9-nonyl amine as a substitute for Plasmochin.

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Search No. 893

CHEMOTHERAPY OF MALARIA

Part V

Acridine Compounds as Antimalarials

by

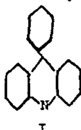
James H Williams

June 1942

<u>Table of Contents</u>

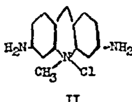
Introduction

The beginning of therapeutic research with compounds of the acridine series may be traced back to the work of Mannaberg in 1897 This worker studied the action of certain dyestuffs, based on the phosphine nucleus (I)



against various types of infective organisms, including the malarial parasite

The above tests, together with those carried out by Kalberlah and Schlossberger in 1918 in which trypaflavin (II)



was found to have no effect in malaria, illus*rate the haphazard character of the meager tests of acridine compounds as antimalarials prior to the extensive researches undertaken by the I G Farbenindustrie pursuant to the War of 1914-1918

As Eisleb (1926) has pointed out, prior to Roehls (1926) elaboration of his now classic method for determining antimalarial activity in birds, the lack of an appropriate test method restricted antimalarial investigation and permitted no rigorous evaluation of such compounds as were synthesized

In view of these facts it is not unexpected that prior to 1926, the main efforts of research workers in the acridine field was directed to the determination of the antiseptic qualities of acridines Such researches were far from fruitless since they led to the discovery of the antibacterial value of compounds such as acriflavine, etc by Browning and Gilmour (1913) and to the discovery of rivanol, by Morgenroth and Co-Workers (1921)

At about the same time that work was being prosecuted on antimalarials of the quinoline group by the I G research staff, interest was also being centered upon replacement of the quinoline nucleus by acridine In 1926 Plasmochin was offered to the world and very soon thereafter Mauss and Mietzsch (D R.P 553,072) patented analogous compounds which were based on acridine as the nitrogen bearing nucleus

Of these compounds the most important from the clinical point of view was Atebrin (III)



III

which soon took and now holds a place in the physicians armamentarium rivalling that held by quinine

Naturally other research workers throughout the world took up the hunt for compounds of a similar nature Of these the Russians under the leadership of Magidson contributed the most Very little has been published in the scientific literature by the German school, concerning the work done at the I G Farbenindustrie For information concerning such work reference must be made to the patent literature

I Arrangement of the Search

The set-up of this section of the search follows much the same lines as section IV Tables are presented in which the compounds are arranged according to the positions occupied by the substituents In these tables test data is provided together with references pertinent thereto Following the tables the relationship between chemical structure and antimalarial activity, if any is apparent, is discussed, and finally, compounds in the series under consideration which reached a point of clinical significance are taken up

The patent literature, as in Part IV, is collected in one place

The bibliography is to be found at the end of the search

II Methods Used in Testing Acridine Antimalarials

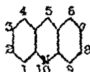
Most of the tests on acridine compounds reported in the literature were carried out on Pl praecox infections in siskins since the drugs proved to be more highly effective as schizonticides than as gametocides

Kikuth (1932) reported that Atebrin, when tested against hemoproteus infections of Bobolinks, was as ineffective as quinine as far as affecting the gametes in the peripheral blood was concerned

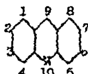
Very little information is available to indicate what specific methods of treatment were actually used However, it is probably safe to assume that the discussion of methods outlined in connection with Part IV of this search applies to the acridine series as it does to the quinolines

III Tabular Presentation of Data Relating to Acridines Having Substituents in Positions 2, 5, and 9

(A) Three methods of numbering the various positions of the acridine nucleus may be found in the literature namely



Used by the French and by Chemical Abstracts prior to 1936



Used by the Germans and Russians and by Chemical Abstracts subsequent to 1936

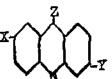
In the present instance use has been made where necessary of the convention adopted by Chemical Abstracts since 1936

(B) In the tables it should be noted that the activity is represented as the reciprocal of the true therapeutic index This is the same procedure followed in earlier sections of the search

(C) The reference numbers relate to the bibliography at the end of the search

Table I

Data Relating to Acridine Antimalarials Having the Structure



X represents	Y represents	Z represents	Test Organism	Host	Activity	References
CH_3O-	Cl	$-NH(CH_2)_2N(C_2H_5)_2$	Pl. praecox	Siskin	CI=8	114
CH_3O-	Cl	$-NH(CH_2)_3N(C_2H_5)_2$ Acrichine No 5	Pl praecox	Siskin	CI=15	108,107, 118, 114, 59, 165
CH_3O-	CN	$-NH(CH_2)_3N(C_2H_5)_2$	Pl praecox	Siskin	CI=10	118, 119
CH_3O-	Cl	$-NHCH_2CH(OH)CH_2N(C_2H_5)_2$	Pl praecox	Siskin	CI=6	114
CH_3O-	Cl	$-NHCH_2CH(OH)CH_2-N\langle(CH_2CH_2)(CH_2CH_2)\rangle CH_2$	Pl praecox	Siskin	+	172, 17
CH_3O-	Cl	$-NH(CH_2)_3-N\langle(CH_2-CH_2)(CH_2-CH_2)\rangle O$				115

(contin:)
Table I

X represents	Y represents	Z represents	Test Organism	Host	Activity	References
CH_3O-	Cl	$-NH(CH_2)_4N(C_2H_5)_2$ Acrichine No 8	Pl praecox	Siskin	CI=20	107, 108, 114, 147
CH_3O-	F	$-NH(CH_2)_4N(C_2H_5)_2$	Pl praecox	Siskin	+	121
CH_3O-	Cl	$-NHCH(CH_3)(CH_2)_2N(C_2H_5)_2$	Pl praecox	Siskins	CI=6 6	108, 114
CH_3O-	Cl	$-NH(CH_2)_5N(C_2H_5)_2$	Pl praecox	Siskins	CI=6	108, 114
CH_3O-	Cl	$-NHCH(CH_3)(CH_2)_3N(C_2H_5)_2$ Atebrin	Pl praecox	Siskin	CI=15	108, 114, 115, 59, 165, 48, 116, 113, 126
CH_3O-	Br	$-NHCH(CH_3)(CH_3)_3N(C_2H_5)_2$	Pl praecox	Siskin	CI=7 5	115
CH_3O-	CN	$-NHCH(CH_3)(CH_2)_3NEt_2$	Pl praecox	Siskin	CI=1	118

(contin)
Table I

X represents	Y represents	Z represents	Test Organism	Host	Activity	Reference
CH_3O-	Cl	$-NH(CH_2)_6N(C_2H_5)_2$	Pl praecox	Siskin	CI=5	114
CH_3O-	Cl	$-NH-CH_2-CH<$ (bicyclic: $CH_2-CH_2-CH_2$, $CH-N$, CH_2, CH_2-CH_2, CH_2)			+	102
CH_3O-	Cl	$-NH-C$ ring: $C(=O)-N-C_6H_5$, $C-N-CH_3$, CH_3			+	8
CH_3O-	Cl	$-NH-C$ ring: $S-C-CH_2CH_2OH$, $N-C-CH_3$			+	8
CH_3O-	Cl	$-NH\ C$ ring: $S-CH$, $N-C-C_6H_5$			+	8
CH_3O-	Cl	$-NH-C_6H_4-SO_2NH-C_6H_4-SO_2NR_2$				38

(contin)
Table I

X represents	Y represents	Z represents	Test Organism	Host	Activity	References
CH_3O-	Cl	$-NH-C_6H_4-SO_2NH_2$				17
CH_3O-	Cl	$-O-C_6H_5$				47
CH_3O-	$-NH_2$	Cl				121
CH_3O-	Br	Cl				115
CH_3O-	CH_3O-	$-NHC_5H_{11}(n)$				81, 82, 83
CH_3O-	CH_3O-	$-N(CH_2-CH_2)_2N$-bis				81, 82, 83
CH_3O-	CH_3O-	$-NHC_3H_7(n)$				81, 82, 83
CH_3O-	CH_3O-	$-NHC_2H_5$				81, 82, 83
CH_3O-	CH_3O-	$-NHCH_3$				81, 82, 83

(contin)

Table I

λ represents	Y represents	Z represents	Test Organism	Host	Activity	References
CH_3O-	CH_3O-	-NHC_4H_9(n)				81, 82, 83
CH_3O-	Cl	-N(CH=N, CH=CH) [ring: -N<CH=N–CH=CH>]				111
CH_3O-	Cl	-NH$(CH_2)_3$N(CH=N, CH=CH) [ring: N<CH=N–CH=CH>]				111
CH_3O-	NO_2	-NHCH$(CH_3)(CH_2)_3N(C_2H_5)_2$			-	150
CH_3O-	NH_2	NH_2				142a

(contin)
Table I

X represents	Y represents	Z represents	Test Organism	Host	Activity	References
C_2H_5O-	Cl	$-NH(CH_2)_2N(C_2H_5)_2$	Pl praecox	Siskin		113
C_2H_5O-	Cl	$-NH(CH_2)_3N(C_2H_5)_2$	Pl praecox	Siskin	CI= 7 5	108, 114, 113
C_2H_5O-	Cl	$-NH(CH_2)_4N(C_2H_5)_2$	Pl praecox	Siskin	CI=11 2	108, 113, 114
C_2H_5O-	Cl	$-NH-CH(CH_3)(CH_2)_3N(C_2H_5)_2$	Pl praecox	Siskin	+	113
C_2H_5O-	NO_2	$-NH(CH_2)_2N(C_2H_5)_2$	Pl praecox	Siskin	CI=0	114, 113
C_2H_5O-	NO_2	$-NH(CH_2)_3N(C_2H_5)_2$	Pl praecox	Siskin	+	113
C_2H_5O-	CN	$-NHCH(CH_3)(CH_2)_3N(C_2H_5)_2$				121
C_2H_5O-	NO_2	$-N\langle^{CH=N}_{CH=CH}$				111

(contin)
Table I

X represents	Y represents	Z represents	Test Organism	Host	Activity	References
CH_3-	Cl	$-NH(CH_2)_3N(C_2H_5)_2$	Pl praecox	Siskin	CI=6	108, 114
CH_3-	NH_2	- (ring) $-NH_2$ Phosphin 2G Vitol Yellow			-	122
CH_3-	Cl	CH_3 $C-N-CH_3$ $-NH-C$ ∥ ∣ $C-N-C_6H_5$ O			+	8
CH_3-	Cl	$S-CH$ $-NH-C$ ∥ $N-C-C_6H_5$			+	8
Cl	Cl	$S-CH$ $-NH-C$ ∥ $N-C-C_6H_5$			+	8
Cl	Cl	$S-C-CH_2CH_2OH$ $-NH-C$ ∥ $N-C-CH_3$			+	8

(contin)

Table I

X represents	Y represents	Z represents	Test Organism	Host	Activity	References
Cl	Cl	$-NH-C$ pyrazolone ring (CH_3, $N-CH_3$, $N-C_6H_5$, $C=O$)			+	8
Cl	Cl	$-NHCH(CH_2)_3N(C_2H_5)_2$ (CH with CH_3)				115
HO-	Cl	$-NHCH(CH_3)_3N(C_2H_5)_2$ (CH with CH_3)				115
$(CH_3)_2NH-$	Cl	$-NHCHCH_2N(C_2H_5)_2$ (CH with CH_3)			+	17
$(CH_3)_2NH-$	Cl	-O-cyclohexyl				17
$(CH_3)_2NH-$	Cl	$-NHCH_2CHCH_2N(C_2H_5)_2$ (CH with OH)			+	17

IV Detailed Discussion of Individual Acridine Antimalarials of the 2, 6, 9 Type

(A) Atebrin
- (1) Historical
- (2) Synthesis of Atebrin
- (3) Physical and Chemical Properties of Atebrin
- (4) Analytical Determination of Atebrin
- (5) Absorption and Excretion of Atebrin
- (6) Pharmacology and Toxicity of Atebrin
    - In Animals
    - In Man
- (7) Dosage of Atebrin in Man
- (8) Therapeutic Activity of Atebrin
    - In Animals and Birds
    - In Man
- (9) Prophylactic Action of Atebrin
- (10) Action of Atebrin
- (11) Atebrin plus Plasmochin in Human Malaria

(B) Atebrin Musonate

(C) Acrichine No 8

(D) Chemiochine

A. Atebrin

(1) Historical

The original synthesis of Atebrin may be attributed to Mauss and Mietzsch of the I G Farbenindustrie who prepared it as part of the extensive program of antimalarial research being carried on there at that time The drug was disclosed in German Patent 553,072 of June 2, 1932 but the formula was not made public until 1933 (Mauss and Mietzsch)

Schulemann (1932) presented the first published report on the compound and this was soon followed by more extensive experimental and clinical data prepared by Kikuth (1932) Sioli (1932), Muhlens (1932), Muhlens and Fischer (1932) and Green (1932)

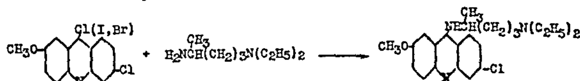
In April of 1932, Acridine was first offered for general sale in Germany but the compound was not accepted by the Council on Pharmacy and Chemistry of the American Medical Association until 1940 (see page 185)

Atebrine has been known by many names Originally it was called Plasmochin E or Erion but these names were soon abandoned in favor of the name by which we now know the drug The French, when they duplicated the compound, called it 866 R P and later Quinacrine or Chinacrine (League of Nations 1937), while the Russians called their equivalent Acrichine (Chelinztzev et al 1934) (Magidson et al 1935)

In the United States Atebrine is manufactured and sold by the Winthrop Chemical Company, Inc under U S P 2 113,357 of April 5, 1938

(2) Synthesis of Atebrine

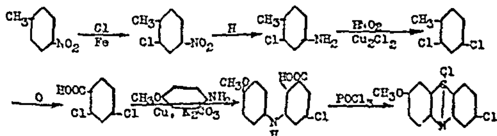
The synthesis of Atebrine follows the following scheme



See - Mauss and Mietzsch (U S P 2,113,357), Knunyantz et al (1934), Winthrop Chemical Co , Inc (1941)

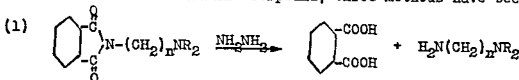
This synthesis, as may be seen involves three parts (A) Preparation of the acridine nucleus (B) Preparation of the dialkylamino alkylene amine (C) Condensation of A and B

The preparation of the acridine nucleus follows the following scheme

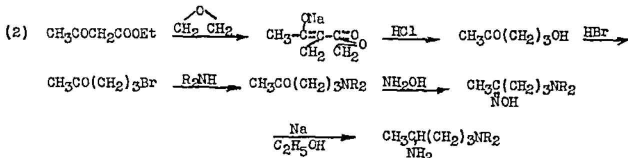


See - Mauss (U S P 1,855,302), Magidson et al (1935) and Knunyantz et al (1934)

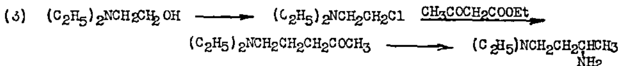
As for the diamino compound, three methods have been outlined



See - Shriner and Upson (1941)



See - Magidson et al (1935), Katznelson et al (1936), Knunyantz et al (1934)



See - Magidson et al (1934), Knunyantz et al (1934), Schulemann, Schönhofer and Wingler (U S P 1,747,531)

(3) Physical and Chemical Properties of Atebrin

Atebrine is obtained as the dihydrochloride, a yellow powder, having a bitter taste and melting at 245-255°C with decomposition (Kikuth 1932) It is soluble in water to the extent of 7% at 40°C (Kikuth 1932) or 2-3% at room temperature (Findley 1939) and in alcohol (Merck 1940) The free base is about one-fifth as soluble as the hydrochloride (Christophers 1937)

When exposed to ultra-violet light Atebrine gives off a brilliant green fluorescence which may be observed in aqueous solution in dilutions of one part in five million (Winthrop 1941)

The dissociation constants of the drug have been determined by Christophers (1937) to be pk_1= 3 88, pk_2= 5 47 and possibly pk_3= 11.0

Fulton (1937) reported the partition coefficient=

$$\frac{\text{Conc drug in Red Cells}}{\text{Conc drug in Serum}}$$

to be 2.2 He postulated the theory that a high ratio should facilitate antimalarial action since such action probably takes place within the red cells In the same series of experiments quinine had a coefficient of 2 3

Atebrine dihydrochloride is stable at room temperature, in the form of a one percent solution it may be kept for three weeks at 37°C without change However, heating the solution to 105°C for fifteen minutes causes decomposition to commence within three days (Mietzsch, Mauss and Hecht 1936) As the decomposition proceeds 2-methoxy-6-chloro acridone precipitates as a yellow powder while the aliphatic portion of the molecule remains in solution Oxidation of the free base with acidic potassium permanganate likewise causes decomposition, the aliphatic t b

5-diethylamino-2-amino pentane (Tschelinov et al (1934))

(4) Analytical Determination of Atebrin

As pointed out by the Winthrop Chemical Co , Inc (1941), the fluorescence of Atebrine provides the simplest means for the detection of the drug, and this is the basis on which most workers have developed their analytical methods.

Fundamentally all methods are much the same The urine is rendered alkaline, the free base is extracted with a suitable water immiscible solvent, the solvent evaporated and the residue dissolved in acidulated water The resulting solution is then neutralized, extracted and the extract compared colorimetrically with standards

In the case of blood or tissue it is of course necessary to destroy or remove the protogenous or other interfering substances

In accord with the above method Tropp and Weise (1933) used hydrochloric acid The extraction may be carried out with ether or amyl alcohol Weise (1937) objected to amyl alcohol because of the possibility of separating other pigments from the residue which might interfere with the test

Hecht (1933) objected to the method of Chopra and Roy (1936) which comprised essentially the drying of oxalated blood on filter paper, extraction with ether followed by the usual steps, and outlined the following method To a given amount of urine, blood or tissue is added an equal quantity of 60% KOH and the mixture heated on a boiling water bath for five minutes Following this an equal quantity of distilled water is added and the solution extracted with a mixture of eight parts of benzene plus two parts of amyl alcohol (2 cc per gram) The extract is centrifuged, 75% of the volume removed and shaken with a measured volume of normal HCl After settling, the mixture is alkalinized and shaken with amyl alcohol This solution is then compared with the standard

In 1937 Chopra and Roy introduced the use of papain to destroy tissue but Gentzkow (1938) claimed that this was not satisfactory if the amount of Atebrine present was small According to Gentzkow a method which is accurate enough to measure differences of Atebrine concentration of 0 1 mgm per liter, comprises adding 5 cc of oxalated blood to 45 cc of acetone with constant shaking After shaking a while longer, 2 cc of aqueous lead acetate is added and the mixture centrifuged to separate the protein precipitate To the supernatant solution is added 5 cc of water, the resulting solution evaporated to 2 cc on a water bath cooled and treated with 0 5 cc of 30% H_3PO_4 and made up to 5 cc After filtering, the filtrate is transferred to a test tube and for each cc 0 1 cc of Tanret's Reagent added After heating on a boiling water bath for five minutes and cooling, a fine white precipitate is obtained which persists for some time

Auerbach (1937) determined Atebrine by precipitating the drug as the dichromate salt following which the excess dichromate was reacted with potassium iodide and the liberated iodine titrated against sodium thiosulfate

More recently Dmitriev (1940) utilized still another method To 1 cc of chloroform in a test tube he added 0 5 cc of body excretion followed by 2 cc of 15% acetic acid To this mixture was then added 1 cc of 10% sodium hydroxide and 0 5 cc of aqueous chloramine with shaking In the presence of Atebrine first the aqueous layer and then the chloroform layer became cherry red This method detects as low as 0 01 mgm of the drug, but is much less sensitive when applied to faeces

Others who have developed or contributed to the development of tests for Atebrine include Green (1932) Watts and Ghosh (1934) and Hicks (1935)

(5) Absorption and Excretion of Atebrin

From the large amount of work done on this phase of Atebrin therapy it appears that when given orally the drug is absorbed via the intestine, passes into the blood stream for a short interval, undergoes partial accumulation in the liver, lungs, kidneys and spleen and is finally excreted via the kidneys and gall bladder The Atebrin excreted by the gall bladder undergoes partial re-absorption through the intestine It is significant that although the drug disappears from the blood stream rapidly, excretion from the body is slow This appears to be characteristic of acridine drugs in general.

Hecht (1933) found that very shortly after mice were given 0 5 cc of a 1% solution of Atebrin dihydrochloride, the drug was more or less diffused through most of the organs of the body After two and one-half hours, it could be detected in the liver, gall bladder and intestinal canal. The gall bladder showed highest fluorescence and for a longer time than any other organ Hecht (1936) also found that when given orally Atebrin rapidly disappears from the blood stream and is stored chiefly in the liver, lungs, kidneys and spleen Chopra et al (1936) confirmed Hecht's findings by reporting that although the drug cannot be detected in the blood for more than twenty-four hours after injection it remains in the body for a long time.

Foy, Kondi and Peristeris (1936) found by fluorescent analysis that the quantity of Atebrin retained depends to some extent upon the intervals at which the drug is given Small doses are eliminated more rapidly, in other words, there appears to be a "potential of excretion" that corresponds to a maximum dose absorbed in a unit of time (twenty-four hours), any quantity in excess of the limit being eliminated more slowly after being more or less temporarily accumulated in the liver, spleen and reticulo endothelial system

Kehar (1935) gave persons 0 3 grams of Atebrin 2HCl and was able to detect traces of the compound in the urine one to one and one-half hours later Excretion may continue for a long time, however, beyond the last dose

Tropp and Weise (1933) gave 0 3 grams Atebrin dihydrochloride per day for seven days The highest daily excretion was 11 7 mgms in the urine, and this decreased progressively to 1 mgm on the 18th day after the drug was discontinued Thonnard-Neumann and Le Doux (1931) detected it in urine 36 days after the last dose, and Jarvis (1932) recorded its presence on an average of 26 days after treatment Massa (1933) using ultra violet radiation to detect Atebrin confirmed its presence even 60-70 days after treatment

Although Tropp and Weise (1933) found 50-70% of Atebrin is excreted in the urine, Kehar (1935) was of the opinion that a considerable portion was transformed in the organism and finally excreted in the form of disintegration products No determination of the amount excreted via the intestines has been made Ashbel (1939) gave 25 cholecystites Atebrin and found that elimination with the bile began two days after treatment, and was complete after 32 days.

(6) Pharmacology and Toxicity of Atebrin

Generally speaking, Atebrin is relatively non-toxic, the therapeutic use of the drug alone in doses of 0 3 grams per day for five to seven days causes hardly any trouble in adults (League of Nations 1937)

In Animals

Hecht (1933) and Dawson et al (1935) reported that large doses of Atebrin in animals caused gastro-intestinal and cerebral irritation Given intravenously some lowering of the blood pressure was noticed For cats, rabbits and mice the oral minimum lethal dose ranged from 0 3-1 0 gram per kg , the intravenous dose being twenty times as toxic as the oral This work was confirmed by Martin, Cominole and Clark (1939)

In cats 2 mgms/kg , given intravenously caused a drop in blood pressure whereas 20 mgms/kg intramuscularly has no action Orally a dose of 0 06 grams/kg is well tolerated (Winthrop 1941)

Chin (1937) studied the action of atebrin on the excised heart of the rabbit and found that the drug caused paralysis due probably to direct action on the heart muscle When given orally to febrile rabbits in dosage of 0 2 grams it caused a temperature drop of one degree over a period of twelve hours This dose constituted about one-half of the minimum lethal dose (Winthrop 1941)

In monkeys de Langen and Storm (1934-1935) found that Atebrin causes a drop in both the systolic and diastolic blood pressure when given intravenously

The same authors also found that small doses of Atebrin caused stimulation of the excised guinea pig uterus while large doses caused stimulation and then paralysis

Clark et al (1939) reported that medication of dogs with 33-66% of the M L D daily for fourteen days resulted in impairment of the hepatic function

In Man

Many reports are available concerning the side effects of Atebrin when administered to human patients When given in excessive doses or over a prolonged period the drug may cause intestinal symptoms, abdominal pains, nausea, vomiting and occasionally diarrhea The nervous symptoms include giddiness, faintness, delirium and fits In children the drug may be regurgitated (Findley 1939)

Ganguli (1933) reported some slight lowering of the blood pressure in man while Chopra et al found little or no evidence of depressing action on the cardiovascular system even when the compound was given to patients with endocarditis or myocarditis Likewise Storm (1935) obtained no effect on the blood pressure by injection of 2 grams of Atebrin

De Langen and Storm (1934) indicated that Atebrin medication does not result in urobilinurea in healthy individuals but it may occur if the liver glycogen is low, due to malnutrition

With respect to the more severe symptoms such as delirium and other psychoses care must be taken to differentiate between oral treatment and intravenous This form of side action may vary from mild excitement to madness resembling delirium tremens In most of such cases the drug was given as Atebrin musonate intravenously and not orally Kingsbury (1934), Briercliffe (1934-1935), Udalagama (1935), Hay, Spaar and Ludovici (1935), Vardy (1935) Van Slype (1936) Van Heukelom et al (1936) and others have made reports concerning the psychoses produced by Atebrin

Probably the most frequently occurring side reaction of Atebrin is yellowing of the skin, which may last for as long as 18 weeks according to Schecter and Taylor (1936)

(7) Dosage of Atebrin in Man

Atebrin is considered substantially non-toxic to man in total doses as high as 4 8 grams save for a transitory yellowing of the skin (Kuhlens and Fischer 1932)

According to the League of Nations Report (1937) agreement

was reached on the dosage of Atebrin, namely, 0 3 grams per day for adults (administered in three doses of 0 10 grams or two doses of 0 15 grams It was recognized that the unit dose per kilogram was not sufficient for all ages Relatively larger doses of atebrin are required during infancy, adult doses often being given to children over fifteen years of age However, in this case the effective dose is slightly toxic

The dosage indicated above is that recommended by the Winthrop Chemical Co (1941) For prophylactic purposes 0 4 grams on one day each week or 0.2 grams on two days each week or 0 05 grams per day is advised.

Intravenously the dose should not exceed 0 1 grams for adults, two or three times daily.

Intramuscularly the same dose as that given orally should be used, although this may be raised to 0 2-0 3 grams for adults if desired

(8) Therapeutic Activity of Atebrin

In Animals and Birds

The first tests of the therapeutic efficacy of Atebrine 2HCl were made by Kikuth (1932) against Pl praecox and Haemoproteus Orizivorae infections in birds When given in suitable dosage the number of parasites was decreased and after about three days the organisms were substantially eradicated When given at the height of the infection the drug caused a reduction in the number of parasites in the blood but did not cause their disappearance.

Coatney (1935) likewise found that in pigeons infected with Haemoproteus columbae the compound had a decided inhibitory effect on growth of young gametocytes, delaying their maturation for as long as fifty-five days.

Krichevskii et al (1935) tested Atebrin (Acrichine) in siskins infected with plasmodium praecox and found that the drug had a therapeutic index of 15 Experiments in monkeys by a number of workers (Knowles and Das Gupta, 1932, Napier and Campbell, 1932, Row et al, 1933 Chopra and Das Gupta, 1933, James (1934), Chopra and Mukherjee, 1936, Mosna, 1936, etc.) indicate that Atebrin has a rapidly destructive action on Pl knowlesi

In Man

Many hundred references to field trials and chemical reports on the use of Atebrin may be found in the literature Perhaps the best review of the action of the drug in human malaria is that of the League of Nations (1937) which is reproduced here in its entirety

"(1) ACTION ON THE TROPHOZOITES —Atebrin in daily doses of 0 30 grm (for adults) has a slightly more rapid action on P VIVAX trophozoites than quinine in the usual dose of 1 grm The trophozoites disappear on an average after the third dose, and in some cases even after the second This parasiticidal action appears to continue for a longer period, in that the phase of latency of the disease (absence of clinical symptoms) is established more certainly and lasts somewhat longer after the end of treatment with atebrin than with quinine On the trophozoites of P MALARIAE, the action of atebrin can be said to be of the same nature On the trophozoites of P FALCIPARUM, atebrin is equally in advance of quinine in certain cases, but the differences between the strains of parasite prevent the drawing of uniform conclusions The trophozoites of P FALCIPARUM disappear from the peripheral blood after the fourth dose of atebrin in 90% of cases.

"(2) THE ACTION OF ATEBRIN ON THE GAMETOCYTES is of a similar nature to that of quinine, it has no effect, from the point of view of devitaliza-

tion, on the gametocytes of P FALCIPARUM But the action on gametocytes already present in the blood is perhaps slightly more marked than that of quinine, particularly as regards the gametocytes of P VIVAX and P MALARIAE

"(3) THE ACTION ON THE CLINICAL SYMPTOMS OF AN ACUTE ATTACK is very marked, both in benign tertian and in malignant tertian In some endemic regions, where there may possibly be special strains of P FALCIPARUM, the therapeutic action of atebrin is even more energetic on malignant tertian than on benign tertian But, in other cases, the contrary seems to be true This is why some practitioners and malariologists in tropical countries prefer to use quinine during the first days of the acute attack and to continue with atebrin thereafter In benign tertian the fever nearly always falls after the first three therapeutic doses of atebrin -- that is to say by the second attack In malignant tertian the fever falls almost invariably by the third attack

"(4) THE ACTION OF ATEBRIN ON RELAPSES is slightly more effective than that of quinine especially in the case of benign tertian and of certain strains of malignant tertian

"(5) THE SPLEEN RATE in communities treated with atebrin seems to decrease somewhat more slowly than in communities treated with quinine, but the effects of the drug continue to be felt for a longer time during the observation period after the end of the treatment, the decrease in the percentage of enlarged spleens continues longer, and the return of the splenic index figures to their former high level occurs a little later

"(6) THE ACTION OF ATEBRIN ON THE GENERAL CONDITION OF PATIENTS seems to be determined by factors which, after this form of treatment, are still not entirely known -- that is to say, by the action of the drug on the organic defenses in general and on the processes of immunization The yellow coloration of the skin produced by atebrin is a disadvantage, especially during prolonged prophylactic treatments "

(9) Prophylactic Action of Atebrin

Napier and Das Gupta (1932) early produced evidence which appeared to indicate that the persistence of Atebrin in the body might render the drug useful as a prophylactic agent

Since then enough information has been forthcoming to establish the prophylactic value of the compound in malarious regions Junge (1933), Soesilo (1934), Bispham (1936) Fischer (1936) Ciuca et al (1937) Hill and Goodwin (1938) Vanselow (1940) etc

James and his Co-workers (1932)(1933)(1936) succeeded in delaying the attack of malaria for as much as thirty-three to thirty-seven weeks after mosquito infection Soesilo, Gilbert and Banguido (1933) were successful in fifteen out of twenty-one cases Dunscombe (1936) carried out tests on 25 employees of the Puerto Rico Sugar Co These persons were given 0 1 grams of Atebrin at 6 P M every second night for three months At the end of the first month two blood smears were positive for Pl falciparum at the end of the second month only one smear was positive The results were considered by Dunscombe, to indicate that Atebrin is a good prophylactic as long as the dose is continued every second night

Ciuca et al (1937) demonstrated that malarial sporozoites under certain conditions are able to withstand atebrin in concentrations of 1 2500 However, they confirmed the results of previous observers that the drug is prophylactic and more constant in its action than quinine

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Bastianelli et al in the League of Nations Report (1937) reviewed the status of Atebrin as a prophylactic, and concluded that daily doses of 0 05 grams of Atebrin were not adequate, further, they pointed out that this dosage cannot be increased for prolonged periods without accentuating the toxic symptoms

Despite the above, however, the Winthrop Chemical Co. (1941) recommends 0 4 grams of the drug once a week as the prophylactic dose.

(10) Action of Atebrin

A certain amount of evidence has been compiled (Nauck and Malamos 1937) which appears to indicate that the action of Atebrin is directly upon the parasite. Fischl and Singer (1935) and Foy, Kondi and Peristeris (1936) determined, from fluorescence studies, that a certain amount of Atebrin in the body localizes in the malarial parasite

James (1934) found that definite morphological changes occurred within the plasmodia of benign tertian and quartan malaria following administration of a single dose of 0 6 grams of Atebrin These changes included aggregation and disappearance, of the pigment, disintegration of the cytoplasm, distention of the nuclear vacuole and opening up and diffusion of the chromatin

Similar changes were noted by Mosna (1936) and Chopra et al (1936) with respect to the action of Atebrin on Pl knowlesi

(11) Atebrin Plus Plasmochin in Human Malaria

As soon as it was established that Atebrin was schizonticidal in its action, and comparable to quinine the use of Atebrin + Plasmochin for the treatment of malaria became popular

Almost immediately the tenor of the clinical reports indicated that the combination was much more effective than either drug alone (Drenowski 1932, Nežic 1933), and further that it stood at the head of all possible combinations used previously (Kirilov-Drenowski 1935)

Napier, Butcher and Das Gupta (1932) were among the first to try the effect of Atebrin plus Plasmochin against malignant tertian and benign tertian malaria They gave 0 1 grams of Atebrin three times daily for four days followed by 0 06 grams of Plasmochin in a three day course The results were excellent and no toxic symptoms were observed

Quite early it was noted that the two drugs could not be administered together since such treatment produced severe toxic reactions (Valcke et al 1933, Chopra et al 1934) Komp and Clark (1935) pointed out that the use of Atebrin with Plasmochin seemed to enhance the toxic qualities of the latter whereas if given separately no reactions were evidenced.

Since the above fact was established the general mode of treatment has followed much the same general pattern For example Ball (1937) used 0 2 grams Atebrin three times daily for four days followed by 0 02 grams of Plasmochin three times daily for four days Nocht and Mayer (1937) suggest seven days Atebrin treatment of 0 3 gram followed by the usual Plasmochin treatment for three to five days.

Council on Pharmacy and Chemistry

REPORT OF THE COUNCIL

T C s k k v c v low g
P N LA L Sec et ry

PURIFIED PROTEIN DERIVATIVE OF TUBERCULIN

Action on Name

Dr F s ond R Lo g inquired of the Council some time ago whether or not the name Purified Protein Derivative would be a ceptable to the Counc l on Pharmacy and Chem stry as a des gnation for the purified prote n princ ple of tubercul n The C u cil voted that t would recognize the name Pur fied Protein Derivat ve of Tuberculin with the understand ng that the in tials P P D which are widely used colloquially will not be used n official designation of the product as on packages or circulars

NEW AND NONOFFICIAL REMEDIES

T s t wi c k e rrxo o
i o t t C P C s
t A s M A soc AT uo N w D
K o c R i A v k w t C h L
s s ON w L v
P N s L Secreta y

AMINOPHYLLINE (See New and Nonofficial Remedies 1940 p 555)

The following dosage forms have been accepted

T bl t Am nophyll ne 0 1 Gm (1Y gr)
Prepa ed by End P oduct Inc R hmond H ll N Y
Amp l Sol t Am nophyll 0 48 Gm 2
P e red b E do P od ct I R hmond H ll N Y
Ampul Solution Am ophyll 0 24 Gm 10
Prep ed by Endo P oduct Inc Richmond H ll N Y
T bl t Am phyll 0 1 Gm (1Y gr n)
P i ed by The Sm h Dorsey Comp y L ncol N b.

ATABRINE di HYDROCHLORIDE.—Chinacr n D hy dr chloride—The d hydrochloride of 3-chloro-7 methoxy 9 (1 n ethyl-4-diethyl am no)butylamino acrid ne—

H CH
N—CH—CH2—CH2—CH2N(C2H5)2
CH3O + HCl + H2O
Cl
N

A t u a d U ses—Atabr ne d hydrochloride destroys the a xual form of Pla mod um vi ax and P malariae but the e s c nts of *P falciparum are more resist nt* It does not induce l molysi or cause damage to the l ver or c rculato y system when used therapeut cally It may cau e ep gastric distress and c a ps but it i of low toxicity when admini tered orally The spl en of chronic malaria is not affected by atab ine d hydro- cl lor de but the acutely enlarged spleen yields though more sl wly th n t quinine Its rel tive ant ialarial val e compared to tl at of qui ine is much debated It is cla med to act more rap dly and to requ e a sho ter p riod f treatment It does not nduce sympton s of cincho i m and it may be u ed during preg iancy Its prophylactic value appears to be bout equal to tl at of qui ne It i absorbed re d ly from the i test ne and is excreted slowly in the urine and feces Wh l it s somet mes injected u tramuscul rly or even intravenously n cases of severe n larial infect on when oral admin strat on is not feasible the int avenou injection is dange ous the inject ons must be made e y lowly (See report of F eld, J W Ni en, J C and Hodgki E P Preventio i of Malaria in Field by Use of Qui n e and Atebr n (Atabrine) Experiments in Cli ical Prophylaxis Bull Health O g n League of Nations 6 236 [April] 1937)

Dosa e—Oral. Adults 0 1 Gm. (1 ½ gra ns) three t mes da ly for five days Ch ldren of 1 to 4 years 0 05 Gm (¾ grain) twice daily for five days or once daily for eight days crushed and suspended in honey or syrup Children of 4 to 8 years 0 1 Gm. (1½ grains) twice daily *for five days or once* daily for eight days Children over 8 years Dosage like that of adults.

Prophylactic Dose Adults 0.2 Gm. (3 grains) twice weekly or 0 05 Gm. (¾ grain) daily Ch ldren 0 05 Gm (¾ grain) every other day

The technic of the intramuscular or ntravenous administra tion must be learned before the method is used Details will *be found in the c rculars of manufacturers* and in various publi cations

Man f ct ed by the Win hrop Chem cal Compa y I c. N w York. U S pa ent 2 113,357 (April 5 1938 exp es 1955) U S. trademark 302 473

Ampul At bri d Hyd ochlorid Powder 0.2 Gm with Amp les 10 cc Steril Distilled Water
Tablet A br di-Hyd ochloride (S gr Coat d) 0 1 Gm (1½ grains)
Tablet Atabrine d Hyd ochlorid 0 1 Gm. (1Y gr)
Tablet Atabrin d Hyd ochlorid 0 05 Gm (¾ gra)

Atabrine d hyd ochloride occ rs an od l ss ora ge-y llow bi ter tast g cry tall e powder conta g tw molecules of w t of cry all ion it melts wi h decompos tion between 245 and 247 C. It solubl w te nd l ghtly sol bl in cetone ethe and benzene Aqueous solution of tabri di-hydrochloride re colored y llow and exh bit yellow green fluorescence

D solve bou 25 mg of tabri d hydrochloride 2 cc f lfuric ac d cover the y llow solut on obta ned w h 0 3 cc. of ri cid a da k red col r develops the zone of contact and, on hak g the sol tion t rns red w h loss of fluorescence.

Dissol 1 Gm. f tab e d-hyd ochlorid 50 cc. f water To 5 cc. port on add 1 cc. of d lute ammonia water only yellow p ecip tate esults Add 5 cc. of myl lcohol t the mixt re nd hake the test t be the amyl alcohol laye contains the f ee base, tabri e.

T the first of fou separate 5 cc portions of the sol tion add 1 cc of me cury bi hlorid solution to the second portion dd 1 cc. of potass um iod de solution the th rd port on add 1 cc. of ammon m th ocy nat solut on and t the fourth portion add 1 cc. of potass um d h omate solution yellow precipitat is produced in each m t re. T another 5 cc. port on add 2 drops of ric acid nd 5 drops f sil er n te solut on white precipitate forms, sol bl cess ammon wat T nother 5 cc port on dd 1 cc. of barium hloride solut on no t rbid y res lts.

The p of solut on mad by d ssol g 1 Gm of tabri di-hydro- hlorid accurately weighed, in boiled nd cooled d tilled water ufficient to mak 100 cc of sol tion between 4 5 and 4 9 t 25 C.

Dry about 1 Gm. of bri d hyd ochl ride accurately weighed to constant weight 100 C. he loss weight hould not be less han 5 5 per cen or more than 7 5 pe cent.

Incinerate 1 Gm of tab ne d hydrochloride the h is negl g ble. Tra fer 1 Gm. of tab ne d hydrochlorid acc ra ly weighed t 100 cc cal brated flask and add 50 cc. f w te When the salt ha d ssolved add lowly 4 5 cc of normal sod m hyd ox de sol on m y w h w l g (od bubble ent pment) and fil to the mark w th w ter F l be solut on i o a dry 250 cc. beaker nd add bout 0 3 Gm. f halogen free decolorizing charcoal S th mi t re nd llow it to tand for fi m utes, then fil r th ough dry paper R ject the first 25 cc of the colorless filtra tak 50 cc. of he rema nder and titrat as d ected und r volumetri method I Official nd Ten t Methods of Analy f the Official Ag cul ral Chem ist ed ion 4 1935 pa 331 The calcul ted con ent of hydrochloric cid hould not be less ha 14 1 pe cen nor mor han 14 6 pe cent.

T n f about 0.75 Gm f t brine d hyd ochl rid ccura ely weighed t 100 cc. cal br ed fl k add 10 cc of w nd 10 cc of sol ion made by d ssol g 26 Gm. of sod m cet nd 26 cc f 40 per cent acetic acid ffi w ter t mak total f 100 cc T he solut on he cal b ted fl k dd 50 cc. f ten h-normal pot ssium d h om te nd w ter t the ma k A oid r bubbl ent p ment M thorou hly nd filt the solut on through dry pape reject g he first 15 cc of the filtrate Transf 50 cc. of the fil ra t glass-stoppered Erlenm yer flask, add 15 cc f hyd ochlor ac d and 20 cc f potass um iod de en sol t on. Stoppe the fl k nd m he con ent b w l g gently Allow the m t r t tand the da k for tw m utes and t te the l be ted iod w h tenth normal sodi m th os lf t Each cubi cent meter of ten h-normal pot ss um d hroma sed eq lent to 0 00 881 Gm. of anhydrous tabrine d hydrochloride. Add 3 mg t the we gh found compensa for herent errors of he method The on ent of anhydrous brine d hyd ochloride hould he not less ha 9 5 pe cent or more han 94 5 pe cent.

PROCAINE HYDROCHLORIDE ABBOTT (See New and Nonofficial Remedies 1940 p 81)

The follow ng additional dosage forms ha e been accepted

Ampoul Proc Hyd ochloride 1% H/L 1Y Ea h 1Y cc conta proca ne hydrochloride U S. P 0 015 Gm sod um chloride nd hem cally pure w er make isoton sol ion

Ampoul P oc Hydrochlorid 2% Epi phri 1 50,000 Sol tion 2 c Each 2 conta proca ne hydrochloride U. S. P 0 02 Gm. (⅓ gr) ep ephrine 0 00004 Gm. (⅙,000 gr) and sod m bi ulfite 0 002 Gm. in isotonic solut on.

BOVINE TETANUS ANTITOXIN (See New and Nonofficial Remedies, 1940 p. 419)

Mulford Biological Laboratories, *Sharp & Dohme Phila delphia*

Lyovac T t A itox (Bovi)—A t t d rived from the blood serum of cattle immun zed ga nst he ox of Bacillus tetani (Clostridium tet) It is packaged by the "Lyovac" process, which consists essentially of rapid f eezi g empera re f below he freez g poi t togethe w h rapid dehydra ion nder h gh acuum w hout

B Atebrin Musonate

Atebrin musonate is the name given to the neutral dimethane-sulfonate of Atebrine prepared by Goissidet and Despois for the I G Farbenindustrie (see U S P 2,092,114), for use wherever injection of Atebrin is indicated

The drug first came into prominence during the Ceylon malaria epidemic of 1935, when Blaze and Simeons (1935) ascertained, in 21 cases, that two successive intramuscular injections of 0 375 gm of the musonate (0 375 grams of Atebrin musonate is equivalent to 0 3 grams of Atebrin) sufficed to control the fever and eradicate parasites from the peripheral blood of malaria victims

Many reports are available indicating generally satisfactory results obtained with this composition (Vardy 1935), (Briercliffe 1935), (Udalagama 1935), Hay, Spaar and Ludovici (1935)), (Field and Niven 1936), (Simeons 1936), (Van Slype 1936), (De 1937) etc

Hicks (1935) tested the compound in monkeys using 0 125 grams in 3 cc of water and observed no deleterious effect on the animal tissues When injected, absorption took place much more rapidly than when given orally

It is important to note, however, that injection of Atebrin is fraught with the possibility of toxic reactions, although such manifestations appear to depend a good deal upon individual idiosyncrasy

Fernando and Wijerama (1935) emphasized the necessity of anticipating toxic reactions, and Briercliffe (1935), Govindaswamy (1936), etc , confirmed the occurrence of reactions ranging from delirium to death

On the other hand, Field and Niven (1936) reported no toxic reactions in 176 cases treated with the musonate.

Seelig and Singh (1936) obtained their best results by giving a subcutaneous injection of 0 75 mgms of adrenaline (1 1000) prior to the administration of 0.375 grams of Atebrin musonate some five hours later, followed by the regular peroral course of 0 1 grams of Atebrin three times daily for five days

Summarizing, although Atebrin musonate has a definite place in the treatment of malaria it has no significant advantage over quinine as a sub-tertian gametocide It compares favorably with any other form of medication given intramuscularly (Field, Niven and Guest 1937) but as in all injection treatment, care is necessary to avoid toxic reactions

C Acrichine No 8

Acrichine No 8 or 2-methoxy-6-chloro-9(diethylaminobutyl-amino) acridine was reported by Magidson et al (1936), Krichevskii et al (1934)(1935), and Rubinstein et al (1937)

Against Pl praecox infections in siskins the compound has a therapeutic index of 20 which indicates a higher activity than Atebrin (C I = 15)

Rubinstein (1936) and Rubinstein et al (1937) used the drug clinically with good results but indicated the necessity of combining its use with a course of Plasmozid for optimum effect The compound was given in dosage of 0 1 gram orally, three times daily for seven days or as the lactate plus dextrose (5-8 cc of a 3% soln) daily for the same period It is interesting to note that Rubinstein irradiated the drug with ultra-violet light before use

Equally positive results were achieved by Dubrowskaya (1937) by intravenous injection of acrichine No 8

In reviewing the reports it should be noted that Rubinstein (1936) refers to irradiated Acrichine No 8 as simply Acrichine However, it is clear that Acrichine per se should be reserved for the diethylamino-

isobutylamino derivative, Acridine

D Chemiochine

This trade name is indicated to refer to 2-hydroxy-6-chloro-9(4-diethylaminobutylamino acridine (De Mauro 1939) The same compound is also reported, but not under this name, by Magidson et al (1938)

De Mauro (1939) reports that its action is prompt on the young merozoites of Pl Vivax and Pl Malariae but less prompt on Pl falciparum The dose reported is 0 1 gram, three times dialy for five to seven days No toxic reactions were observed and the fever of spring tertian and quartan malaria subsided rapidly The lowering of the temperature was less marked in fall tertian

V Relation Between Therapeutic Activity and Chemical Structure of the 2 6, 9 Substituted Acridines

In view of the relative paucity of correlated test data on the acridines it is difficult to draw very many tenable conclusions with respect to the relationship between the structure and the therapeutic properties of the active compounds

However, the data which are available will be taken up under the following headings

(A) Effect of Variations in the Dialkylamino alkylene amino group in position 9.

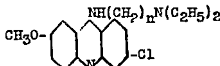
(B) Effect of Changing the Group in Position 2

(C) Effect of Changing the Group in Position 6.

Substantially all the therapeutic results upon which this review is based are taken from the papers published by the Russian School of Workers

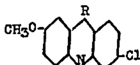
(A) Effect of Variations in the Dialkylamino alkylene amino group in Position 9

Using the data of Magidson et al (1936) respecting the structure



reference to Fig 1 clearly demonstrates the effect of varying the length of the dialkyl amino alkylene amino chain Curiously enough in this instance the alternation which was observed when the same variation was carried out in the quinoline series, is totally lacking The therapeutic activity rises sharply to a maximum when n=4 and then just as sharply declines as the chain length is further increased

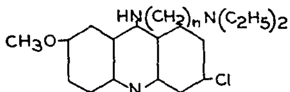
The effect of replacing an hydrogen on the carbon in the chain adjacent the acridine nucleus by a methyl group appears to have a dystherapeutic effect as may be seen from the following table where the base formula may be represented as



R	Therapeutic Index
$-HNCH_2CH_2CH_2CH_2N(C_2H_5)_2$	20
$-HNCHCH_2CH_2CH_2N(C_2H_5)_2$ (with CH_3 on the CH)	15
$-HNCH_2CH_2CH_2N(C_2H_5)_2$	15
$-HNCHCH_2CH_2N(C_2H_5)_2$ (with CH_3 on the CH)	6.6

Likewise, the replacement of one of the hydrogen atoms in the chain by an hydroxyl group has a dystherapeutic effect as may be seen from the

EFFECT OF CHANGING THE WEIGHT OF THE DIALKYLAMINO ALKYL AMINO GROUP IN



ORGANISM - PL PRAECOX
HOST - SISKINS

THERAPEUTIC INDEX →

20
15
10
5

1 2 3 4 5 6

n →

FIG 1

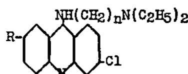
table below in which the same basic structure as that above is assumed

R	Therapeutic Index
$-HNCH_2CH_2CH_2N(C_2H_5)_2$	15
$-HNCHCH_2CH_2N(C_2H_5)_2$ (with OH on CH)	6

It should be observed that replacement of the dialkylamino alkylene chain by heterocyclic structures bearing nitrogen in the ring resulted in active compounds as for example the 2-methoxy-6-chlor-9-lupinyl amino acridine and various 2-methoxy-6-chlor-9-thiazylamino acridines Specific data on these compounds is lacking, however, with respect to the lupinyl compound the expression "strong antimalarial properties" was used.

(B) <u>Effect of Changing the Group in Position 2.</u>

Using for illustration the basic structure



where n=3 a methoxy group in place of R appears to be optimum as may be seen from the following table

R	Therapeutic Index
CH_3O-	15
C_2H_5O-	7.5
CH_3-	6

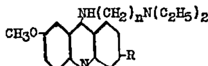
likewise when n=4 the same thing holds

R	Therapeutic Index
CH_3O-	20
C_2H_5O-	7.5

Magidson and Travin (1936) discussing such substitution also state that the introduction of a methyl mercapto group in the 2 position in place of a methoxy group had a negative biological effect, the toxicity of the compounds being increased 3 5 times while the therapeutic action decreased to 2/3 of the original

(C) <u>Effect of Changing the Group in Position 6</u>

Using as the standard the basic structure



where n=3 the effect of changing R may be seen from the table below

R	Therapeutic Index
-	0
NO_2	2 5

(contin)

(contin)

R	Therapeutic Index
CN	10
Cl	15

when n=4

R	Therapeutic Index
Cl	20
F	-

VI. Tabular Presentation of Data Relating to Acridine Antimalarials Having Substituents in Positions Other than 2, 6, 9

This part of the search includes Tables II to XXII arranged as follows

(A) Mono-Substituted Acridines

Table	II	III	IV
Substituents	2	4	9

(B) Di-Substituted Acridines

Table	V	VI
Substituents	2,9	3,9

(C) Tri-Substituted Acridines

Table	VII	VIII	IX	X	XI	XII
Substituents	2,7,9	1,4,9	2,4,9	2,6,8	1,4,6	3,6,10

(D) Tetra-Substituted Acridines

Table	XIV	XV	XVI	XIII	XVII	XVI
Substituents	2,4,6,9	2,4,5,9	2,3,7,9	2,4,7,9	2,6,9,10	2,3,

(E) Tetra-Hydro Acridines

Table	XIX	XX	XXI	XXII
Substituents	9	2,6,9	2,9	3,9

Table II

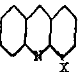
Data Relating to Acridine Antimalarials Having the Structure



X represents	Test Organism	Host	Activity	References
CH_3O				47

Table III

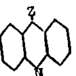
Data Relating to Acridine Antimalarials Having the Structure



X represents	Test Organism	Host	Activity	References
$-NH(CH_2)_2N(C_2H_5)_2$				35
$-NHCH_2-C_6H_{10}-NH_2$ (ring drawn)				35
$-NHCH(CH_3)(CH_2)_3N(C_2H_5)_2$				35

Table IV

Data Relating to Acridine Antimalarials Having the Structure



X represents	Test Organism	Host	Activity	References
$-NHCOCH_2Cl$				130
$-N(CH_3)-CO-C_6H_{11}$				130
$-NHCH_2CH_2N(CH_3)_3$				130
$-NH(CH_2)_2N(CH_2-CH_2-CH_2-CH_2-CH_2)$				130
$-NH(CH_2)_3N(C_2H_5)_2$			CI=0	114
$-OC_6H_5$				6

(contin.)
Table IV

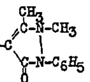
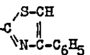
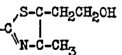
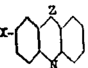
X represents	Test Organism	Host	Activity	References
				8
				8
				8

Table V

Data Relating to Acridine Antimalarials Having the Structure



X represents	Z represents	Test Organism	Host	Activity	References
CH_3O-	$-NH(CH_2)_2N(C_2H_5)_2$				71
CH_3O-	$-NH(CH_2)_3N(C_2H_5)_2$				6, 71
CH_3O-	$-NH(CH_2)_4N(C_2H_5)_2$				6
CH_3O-	$-NHCH(CH_3)(CH_2)_3N(C_2H_5)_2$			- +	58 17
CH_3O-	$-N(C_3H_7)(CH_2)_2N(C_2H_5)_2$				71
CH_3O-	$-N(CH_3)(CH_2)_2N(C_2H_5)_2$				71

(contin)
Table V

X represents	Z represents	Test Organism	Host	Activity	References
CH_3O-	$-O-C_6H_{11}$ (cyclohexyl ring)				6
CH_3O-	Cl				53
CH_3O-	$-NH$ (ring fused with $-N-C(-NH_2)-S-$)				47
CH_3O-	NH_2				52
CH_3O-	$-NCH_3$				52
CH_3O-	$-NH-C_6H_{11}$ (cyclohexyl ring)				52
CH_3O-	$-N(CH_2-CH_2)_2CH_2$ (ring)				52
C_2H_5O-	$-NH(CH_2)_3N(C_2H_5)_2$			+	113

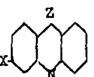
(contin)

Table V

X represents	Z represents	Test Organism	Host	Activity	References
$(CH_3)_2NH-$	$-NHCH_2CH(OH)CH_2-N\langle(CH_2-CH_2)(CH_2-CH_2)\rangle CH_2$			-	17
$(CH_3)_2NH-$	$-NHCH_2CH(OH)CH_2-N(C_2H_5)_2$			-	17
$(CH_3)_2NH-$	$-NHCH(CH_3)(CH_2)_3N(C_2H_5)_2$			-	17
$(CH_3)_2NH-$	-O-⬡				17
CH_3-	-O-⬡				51
CH_3-	-O-⬡-$N(CH_3)_2$				46a
CH_3-	-NH-⬡(N, S ring)C-NH_2				47

Table VI

Data Relating to Acridine Antimalarials Having the Structure



X represents	Z represents	Test Organism	Host	Activity	References
$-C_6H_4-N(CH_3)_2$	$-SO_2-C_6H_4-N(CH_3)_2$				142

Table VII

Data Relating to Acridine Antimalarials Having the Structure

X-(acridine)-Y, with Z at position 9 (N in ring)

X represents	Y represents	Z represents	Test Organism	Host	Activity	References
CH_3O	Cl	Cl				58, 53
CH_3O	Cl	$-NH(CH_3)_3N(C_2H_5)_2$	Pl praecox	Siskin	CI=2	58, 59, 108
CH_3O	Cl	$-NHCH(CH_3)(CH_2)_3N(C_2H_5)_2$	Pl praecox	Siskin	CI=2	58, 59, 108
CH_3O	Cl	$-NHCH_2CH(OH)CH_2N<(CH_2-CH_2)(CH_2-CH_2)>CH_2$				52
CH_3O	Cl	$-N<(C(=O)-C(CH_3))(N(C_6H_5)-C-CH_3)$				52

(contin)
Table VII

X represents	Y represents	Z represents	Test Organism	Host	Activity	References
CH_3O-	Cl	-NH-(cyclohexyl ring)-OCH_3				52
CH_3O-	Cl	-O-(cyclohexyl ring)				51
CH_3O-	NO_2	$-NH(CH_2)_3N(C_2H_5)_2$	Pl praecox	Siskin	CI=2 5	108
CH_3O-	NO_2	$-NHCH_2CH(OH)CH\ N(C_2H_5)_2$	Pl praecox	Siskin	CI=4	108, 114
CH_3O-	NO_2	$-NH-CH_2CH(OH)CH_2N<(CH_2-CH_2, CH_2-CH_2)>CH_2$				17
CH_3O-	NO_2	$-NH-C$ (ring: $S-C-CH_2CH_2OH$, $N-C-CH_3$)			+	8
CH_3O-	NO_2	$-NHC$ (ring: CH_3, $C=N-CH_3$, $C(=O)-N-C_6H_5$)			+	8

(contin)
Table VII

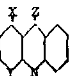
X represents	Y represents	Z represen+s	Test Organism	Host	Activity	Reference
CH_3O-	NO_2	$-NH-C$ (S-CH, =N-C-C_6H_5 ring)			+	8
CH_3O-	NO_2	-O-[ring]				51
CH_3O-	NO_2	-NH-[ring]				52
CH_3O-	NO_2	-NH-[ring]-OCH_3				52
CH_3O-	NO_2	Cl				53
CH_3O-	$-SO_2NR_2$	$-NH(CH_2)_nN(C_2H_5)_2$				9
CH_3O-	$-SO_2NH-$[ring]$-SO_2NR_2$	$-NH(CH_2)_nN(C_2H_5)_2$				38
C_2H_5O-	NO_2	$-NH(CH_2)_2N(C_2H_5)_2$	Pl praecox	Siskin	+	113

(contin)
Table VII

X represents	Y represents	Z represents	Test Organism	Host	Activity	References
C_2H_5O-	NO_2	$-NH(CH_2)_3N(C_2H_5)_2$	Pl praecox	Siskin	+	113
C_2H_5O-	NO_2	$-NHCH_2CH(OH)CH_2N(C_2H_5)_2$	Pl praecox	Siskin	+	113
CH_3-	NO_2	-⬡ $N(CH_3)_2$				46a
C_2H_5-	NO_2	$-NH(CH_2)_2N(C_2H_5)_2$	Pl praecox	Siskin	CI=1.5	114

Table VIII

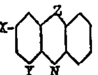
Data Relating to Acridine Antimalarials Having the Structure



X represents	Y represents	Z represents	Test Organism	Host	Activity	References
Cl	Cl	$HN(CH_2)_3N(C_2H_5)_2$				71
NO_2	CH_3O	$-NHCH_3$				17
NO_2	CH_3O	Cl				53

Table IX

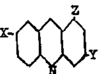
Data Relating to Acridine Antimalarials Having the Structure



X represents	Y represents	Z represents	Test Organism	Host	Activity	References
Cl	Cl	$HNCH_2CH_2N(C_2H_5)_2$				71
Cl	Cl	$HN(CH_2)_3N(C_2H_5)_2$				71
CH_3	Br	$HNCH_2CH_2N(C_2H_5)_2$				71
CH_3	Br	$NH(CH_2)_3N(C_2H_5)_2$				71

Table X

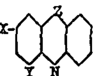
Data Relating to Acridine Antimalarials Having the Structure



X represents	Y represents	Z represents	Test Organism	Host	Activity	References
CH_3O-	Cl-	$HN(CH_2)_3N(C_2H_5)_2$			+	119
CH_3O-	CN	$HN(CH_2)_3N(C_2H_5)_2$			+	119
CH_3S-	CN	$HN(CH_2)_3N(C_2H_5)_2$			±	119

Table IX

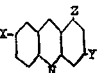
Data Relating to Acridine Antimalarials Having the Structure



X represents	Y represents	Z represents	Test Organism	Host	Activity	References
Cl	Cl	$HNCH_2CH_2N(C_2H_5)_2$				71
Cl	Cl	$HN(CH_2)_3N(C_2H_5)_2$				71
CH_3	Br	$HNCH_2CH_2N(C_2H_5)_2$				71
CH_3	Br	$NH(CH_2)_3N(C_2H_5)_2$				71

Table X

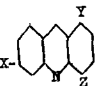
Data Relating to Acridine Antimalarials Having the Structure



X represents	Y represents	Z represents	Test Organism	Host	Activity	References
CH_3O-	Cl-	$HN(CH_2)_3N(C_2H_5)_2$			+	119
CH_3O-	CN	$HN(CH_2)_3N(C_2H_5)_2$			+	119
CH_3S-	CN	$HN(CH_2)_3N(C_2H_5)_2$			±	119

Table XI

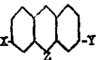
Dat Relating to Acridine Antimalarials Having the Structure



X represents	Y represents	Z represents	Test Organism	Host	Activity	References
$(CH_3)_2N$	Cl	$HNCH(CH_2)_2N(C_2H_5)_2$ CH_3			+	172

Table XII

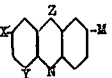
Data Relating to Acridine Antimalarials Having the Structure



X represents	Y represents	Z represents	Test Organism	Host	Activity	References
NH_2	NH_2	$-HSO_4$			-	72

Table XIII

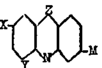
Data Relating to Acridine Antimalarials Having the Structure



X represents	Y represents	Z represents	M represents	Test Organism	Host	Activity	References
Cl	Cl	$HN(CH_2)_3N(C_2H_5)_2$	Cl				71
Cl	Br	$HN(CH_2)_3N(C_2H_5)_2$	Cl				71
CH_3	Br	$NH(CH_2)_3N(C_2H_5)_2$	Cl				71

Table XIV

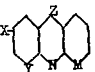
Data Relating to Acridine Antimalarials Having the Structure



X represents	Y represents	Z represents	M represents	Test Organism	Host	Activity	References
CH_3O-	NH_2	$NHCH(CH_3)(CH_2)_3N(C_2H_5)_2$	Cl			-	103
CH_3O-	$-NH(CH_2)_3N(C_2H_5)_2$	$NHCH(CH_3)(CH_2)_3N(C_2H_5)_2$	Cl			-	103
CH_3O-	NO_2	$NHCH(CH_3)(CH_2)_3N(C_2H_5)_2$	Cl			±	103

Table XV

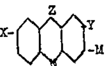
Data Relating to Acridine Antimalarials Having the Structure



X represents	Y represents	Z represents	M represents	Test Organism	Host	Activity	References
CH_3O-	NO_2		NO_2				169

Table XVI

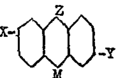
Data Relating to Acridine Antimalarials Having the Structure



X represents	Y represents	Z represents	M represents	Test Organism	Host	Activity	References
CH_3O-	NO_2	$HNCH(CH_2)_3N(C_2H_5)_2$ (with CH_3 on CH)	Cl	Pl praecox	Siskin	CI=3 3	115
CH_3O-	Cl	$HNCH(CH_2)_3N(C_2H_5)_2$ (with CH_3 on CH)	Cl	Pl praecox	Sparrows Finches	CI=6 +	58 59
CH_3-	CH_3	-(cyclohexane ring)-NH_2	NH_2			-	122
CH_3O-	NO_2	$-NH(CH_2)_3NEt_2$	Cl				115
C_2H_5O-	NO_2	$NH(CH_2)_3NEt_2$	NO_2				113

Table XVII

Data Relating to Acridine Antimalarials Having the Structure

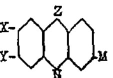


X represents	Y represents	Z represents	M represents	Test Organism	Host	Activity	References
CH_3O	CH_3O	$NH(CH_2)_2NH$-bis	-Cl -I -OH				81, 82, 83
CH_3O	CH_3O	$N(COCH_3)$-C_6H_4-OC_2H_5(p)	-Cl -I -OH				81, 82, 83
CH_3O	CH_3O	$NH(CH_2)_2NH_2$	-Cl -I -OH				81, 82, 83
CH_3O	CH_3O	NH-C_6H_4-NH_2	-Cl -I -OH				81, 82, 83
CH_3O	CH_3O	NH-C_6H_4-CH_3	-Cl -I -OH				81, 82, 83

(contin)
Table XVII

X represents	Y represents	Z represents	M represents	Test Organism	Host	Activity	References
CH_3O	CH_3O	-NH-cyclohexyl (ring drawn)	-Cl -I -OH				81, 82, 83

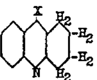
Data Relating to Acridine Antimalarials Having the Structure



X represents	Y represents	Z represents	M represents	Test Organism	Host	Activity	References
CH_3O	CH_3O	$HN(CH_2)_3N(C_2H_5)_2$	Cl	Pl praecox	Siskin	CI=0	108, 114
CH_3O	CH_3O	$HNCH(CH_3)(CH_2)_3N(C_2H_5)_2$	Cl	Pl praecox	Siskin	CI=0	108

Table XIX

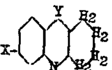
Data Relating to Acridine Antimalarials Having the Structure



X represents	Test Organism	Host	Activity	References
$-CON(C_2H_5)_2$				120
$-CONH(CH_2)_2N(C_2H_5)_2$				120
$-COO(CH_2)_2N(C_2H_5)_2$				120
$-NH(CH_2)_4N(C_2H_5)_2$				6

Table XXII

Data Relating to Acridine Antimalarials Having the Structure

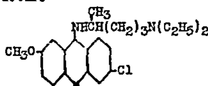


X represents	Y represents	Test Organism	Host	Activity	References
Cl	$NHCH(CH_3)(CH_2)_3N(C_2H_5)_2$ Acridine 36				120
NO_2	$NHCH(CH_3)(CH_2)_3N(C_2H_5)_2$ Acridine 37				120

VII Discussion of Acridine Antimalarials Having Substituents in Positions Other than 2, 6, 9

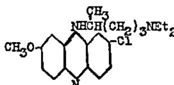
From the above tables a few points of interest may be derived

Using the structure



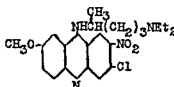
which has a therapeutic index of 15 for comparative purposes

(1) Shifting the halogen from position 6 to position 7 has a effect i e



has an index of 2

(2) Adding a nitro group to the first mentioned structure in position 7 has a dystherapeutic effect also i e



has an index of 3 3

(3) Adding a chlorine atom in position 7 of the Atebrin structure, a product with an index of 6 is formed

Aside from the above there does not appear to be anything of particular interest in any of the groups of compounds beyond the 2,6,9 substituted derivatives

VIII Miscellaneous Antimalarial Compounds of the Acridine Series

(A) Tebetren

(B) Crinodora

(C) Peracrina

A Tebetren (Malarcan)

Tebetren comprises special preparations prepared for Chemopharm, Ltd by Howard & Sons, Ltd of London (Barrowman 1933) and constitutes a combination of methyl acridine dehydrocholate with methyl hydrocupreine and quinidine respectively (Nocht & Mayer 1937, Chopra 1938, Green 1934).

Chopra and Ganguli (1935) found Tebetren capable of controlling fairly heavy infections of Pl Knowlesi in monkeys if given intramuscularly in doses of 4 5-6 grains daily for two days.

Stoute (1932) pointed out that the bile salt served to cut the toxicity of the acridine drugs on intramuscular injection, but observed sloughing when intravenous therapy was tried.

The drug was also tried by Chopra (1933) but generally speaking the compositions proved to be more costly than quinine and yet no more effective than the latter (Manson 1936 and Chopra 1937) Furthermore, it was totally unable to stop the development of the gametocytes of Pl malariae in A Stephensi even when as many as 15 doses of the drug were given

B. Crinodora

This acridine compound, the formula of which does not appear to be available, was first prepared in Italy as a substitute for Atebrin Chopra et al (1940) tried the drug on 44 patients, using 0 1 gram three times daily for five days By this treatment the fever was controlled and the parasites eradicated with the exception of the gametocytes of Pl falciparum. These workers consider the drug to be an excellent substitute for Atebrin.

C Peracrina

According to Fischl and Schlossberger (1933) the name Peracrina was given to a trypaflavin- protein mixture The composition was used more or less successfully in malaria (Luescher 1926, Walker 1924) Berger (1926) felt that it was non-toxic but not superior to quinine, a reaction which was shared by Sinton, Bird and Eate (1927).

IX Patent Literature

The patent literature has been arranged as follows

(A) United States Patents

(B) German Patents

(C) British Patents

(D) Russian Patents

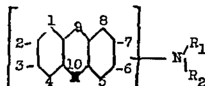
(E) Miscellaneous

United States Patents

U S P. 1,760,781
May 27, 1930

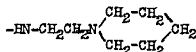
Schulemann, Schönhofer and Wingler
Assigned to Winthrop Chemical Co , Inc.

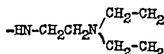
Relates to compounds of the general formula

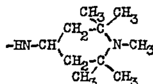


where the nucleus may be further substituted, R_1 represents hydrogen, an alkyl group and amino alkyl group or any other monovalent substituent and R_2 represents an alkylene residue which is substituted by a heterocyclic residue containing nitrogen or by a hydro-aromatic residue which is substituted by a primary, secondary or tertiary amino group

Discloses as examples acridine with the following residues in the 4 position



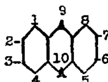




U S P. 1,766,403
June 24, 1930

Schulemann, Wingler and Mietzsch
Assigned to Winthrop Chemical Co , Inc
Corresponds to D R P. 488,890
(Addition to 486,079, 486,771)
also see D R P 488,945
(Addition to 486,079, 486,771)

Discloses diazine, oxazine, thiazine, acridine and xanthene compounds of the formula



wherein one A represents an element of the group N, S and O and the other A represents an element of the group C and N having as a substituent the

group

$$X-N-R_1-N\begin{matrix}R_2\\R_3\end{matrix}$$

wherein X represents hydrogen, an alkyl group or other monovalent substituent, R_1 an alkylene residue, R_2 hydrogen or an alkyl, R_3 an alkyl group.

In the acridine series the disclosures constitute acridine having the following substituents

Position -	2	3	4	-
	-	-	$NHCH_2CH_2N(C_2H_5)_2$	-
	CH_3	-	$NHCH_2CH_2N(C_2H_5)_2$	-
		H_2N	-	$NHCH_2CH_2N(C_2H_5)_2$
	-	$NHCH_2N(C_2H_5)_2$	-	$NHCH_2CH_2N(C_2H_5)_2$

U.S.P. 1,855,302
April 26, 1932

Lauss
Assigned to Winthrop Chemical Co. Inc.
Corresponds to D.R.P. 5[illegible]

This patent relates to compounds of the formula

alkyl-O- [acridine] -Hal, with Hal at position 9

and process of preparing the same

Discloses preparation according to the procedure

alk-O-C_6H_4-NH_2 + HOOC-, Hal-C_6H_3-Hal → alk-O-C_6H_3-NH-C_6H_3(COOH)-Hal

→ alk-O-(diphenylamine)(COOH)-Hal → alk-O-(acridone, C=O)-Hal

→ alk-O-(acridine, 9-Hal)-Hal

U S P 1,889,704
November 29, 1932

Schulemann, Mietzsch and Wingler
Assigned to Winthrop Chemical Co., Inc.

Discloses acridines of the general structure

(next

where X stands for hydrogen, which may be substituted, for example, by an alkyl group, an aminoalkyl group, or a substituted aminoalkyl group, such as an alkylaminoalkyl group or a dialkylaminoalkyl group, R_1 stands for an alkylene radical, in which the hydrogen atoms may be substituted by a hydroxy group, R_2 and R_3 stand for hydrogen or alkyl groups which may be substituted for example, by an amino group, n stands for one of the numbers one or two and wherein the acridine nucleus may be further substituted by alkyl, alkoxy, phenyl, halogen and the like.

As examples, they give the following acridines

Position - 2	3	4	7	9
0	$HN(CH_2)_2N(C_2H_5)_2$	0	$HN(CH_2)_2N(C_2H_5)_2$	0
0	0	$HN(CH_2)_2N(C_2H_5)_2$	0	0
CH_3-	0	$HN(CH_2)_2N(C_2H_5)_2$	0	0
C_2H_5O	0	0	0	$HNCH_2$-$CHOH$ $CH_2N(C_2H_5)_2$
0	0	0	0	$N(CH_2)_2NC_2H_5$ C_2H_5

(See below)

U S P 1,962,277
June 12, 1934

Jensch
Assigned to Winthrop Chemical Co , Inc

Relates to 9-amino acridine derivatives of the general type

in which at least one of the X's stands for a nitro group, and at least one of the other X's stands for hydrogen, halogen, amino, alkyl and alkoxy

Specific examples cited are the following

Position - 2	3	6	9
C_2H_5O-	-	NO_2	$-NHCH_2CH_2N(C_2H_5)_2$
C_2H_5O-		NO_2	$-NHCH_2CHCH_2N(C_2H_5)_2$ (OH on CH)
C_2H_5O-		NO_2	-NH-⬡-$NH(CH_2)_2N(C$...
C_2H_5O-		NO_2	-NH-⬡-$NHCH_2CH$-OH, $CH_2-N(C$...
C_2H_5O-		NO_2	-NH-⬡-$NHCH_2$-CHOH, CH_2, NH, $(CH_2)_2-N(C$...
C_2H_5O-	NO_2	NO_2	-NH-⬡-$OCH_2CH_2N(C_2H_5)_2$
CH_3O-		NO_2	$-NHCH_2CHCH_2N(C_2H_5)_2$ (OH on CH)
-		NO_2	$-NHCH_2CHCH_2N(CH_3)_2$ (OH on CH)
C_2H_5O-		NO_2	$-NHCH_2CONH(CH_2)_2N(C_2H_5$
C_2H_5O-		NO_2	

also 2-ethoxy-7-nitro-9(β-diethylamino-β-hydroxypropyl acridine

1-methoxy-4-methyl-6-nitro-9(γ-diethylamino-β-hydroxy propyl amino) acridine

1,2-dimethoxy-4-methyl-6-nitro-9(γ-diethylamino-β-hydroxy propyl amino) acridine

U S P 2,041,436
May 19, 1936

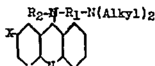
Schulemann and Schönhofer
Assigned to Winthrop Chemical Co , Inc

Relates to method of stabilizing aqueous solutions of basic heterocyclic nitrogen compounds selected from the group quinoline acridine thiazine and diazine compounds comprising the addition of a small amount of a water soluble sulfhydryl compound and particularly sodium thioglycolate

U S P 2,077,249
April 13, 1937

Mietzsch and Mauss
Assigned to Winthrop Chemical Company Inc
Corresponds to D R P 631,504, E P 441,007, E P 363,392

Discloses the preparation of compounds of the general type



in which R_1 stands for an aliphatic radical such as methylene, ethylene, propylene, hydroxy propylene group and the like, R_2 stands for hydrogen or an alkyl group such as methyl or ethyl and X stands for a substituent

selected from alkyl groups and halogen atoms

According to the specification compounds such as 2-chloro-9-(alpha-diethyl-delta-pentylamino) acridine and the corresponding 2-methyl and 2-ethyl derivatives are prepared by reacting upon acridine substitution products which contain in the 9 position a replaceable substituent and in the 2 position a halogen atom or an alkyl group, with aliphatic polyamines containing a primary or secondary amino group Replaceable substituents in the 9 position may be ether and ester-like groups such as halogen, amyloxy, alkoxy, aryl and alkylmercapto groups

U S P 2,079,023 May 4, 1937

Mauss and Mietzsch
Assigned to Winthrop Chemical Co , Inc

This patent relates to the preparation of compounds of the 9-amino, 10-alkyl or 9-amino 10-aralkyl acridinium type in which the 9-amino group is further substituted by an aliphatic amine radical.

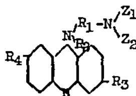
Compounds of this type which are disclosed include

9-(alpha-diethylamino-delta-pentylamino)-10-methyl acridinium chloride
9-(diethylaminoethylamino)-10-methyl acridinium hydroxide
9-(alpha-diethylamino-delta-pentylamino)-10-benzyl acridinium citrate
6-chloro-9-(alpha-diethylamino-delta-pentylamino)-10-methyl acridinium chloride
6-chloro-9-(alpha-dimethylamino-delta-butylamino)-10-butyl acridinium chloride and several others.

U S P. 2,082,171 June 1, 1937

Mietzsch and Mauss
Assigned to Winthrop Chemical Co , Inc.

Discloses acridine compounds having the structure



wherein R_1 stands for an organic radical of the alkylene or phenyl alkylene series, the carbon chain of which may contain nitrogen, oxygen or sulfur atoms as interrupting members R_2 stands for hydrogen or alkyl, Z_1 and Z_2 stand for hydrogen, alkyl, amino, or alkyl amino alkyl, or jointly form with the adjacent N a ring of the piperidine type, the group $-N\langle^{Z_1}_{Z_2}$ being attached to R_1 at least once, R_3 stands for halogen or alkyl and R_4 stands for an alkyl mercapto group

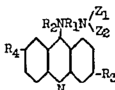
Specific compounds disclosed include

2-methylmercapto-6-chloro-9(α-diethylamino-δ-pentylamino) acridine
2-methylmercapto-6-chloro-9(α-diethylamino-δ-butylamino) acridine
2-methylmercapto-6-chloro-9(β-diethylamino ethoxy ethyl amino) acridine
2-methylmercapto-6-chloro-9(β-diethylamino ethyl mercapto ethyl amino) acridine
2-methylmercapto-6-chloro-9(α-diethylamino-γ-propyl amino) acridine
2-methylmercapto CH_3-9(α-diethylamino-δ-pentylamino)
2-methylmercapto CH_3-9(α-diethylamino-β,β-dimethyl-γ-propyl amino) acridine
CH_3O- CH_3-9(α-diethylamino-ψ-pentylamino) acrid
C_4H_9O- Cl 9(α-diethylamino-δ-pentylamino)
$C_8H_{17}O$- Cl 9(α-diethylamino-δ-pentylamino) acri

U S P 2,083,171 June 1, 1937

Mietzsch and Mauss
Assigned to Winthrop Chemical Co , Inc

Various details are given of the production of of the general formula



where R_1 stands for an organic radical of the alkylene or phenylalkylene series including those substituted by hy, and the carbon chain of which contains as an interrupting member a nitrogen oxygen or sulfur atom R_2 stands for hydrogen or alkyl, Z_1 and Z_2 stand for substituent hydroger alkyl, aminoalkyl, alkylaminoalkyl or alkylene groups, the alkylene group standing jointly for Z_1 and Z_2, the group $-N\langle^{Z_2}_{Z_1}$ being attached to R_1 at least once, R_3 stands for hydrogen or alkyl, and R_4 stands for an alkyl- group

Several examples are given, of which the following are claimed specifically

Position -	3	5	8
	CH_3S-	$HNCH(CH_2)_3N(C_2H_5)_2$ (CH₃ on CH)	Cl
	CH_3S-	$HNCH(CH_2)_3N(C_2H_5)_2$ (CH₃ on CH)	CH_3

U S P 2,092,114 September 7, 1937

Goissedet and Despois,
Assigned to Winthrop Chemical Co , Inc.

Soluble salts suitable or intram

injection are prepared by causing basically substituted amino acridines to react with alkyl sulfonic acids, or by double decomposition as by reaction of the sulfate of dialkyl aminoalkyl amino acridine with the barium salt of an alkyl sulfonic acid Basically substituted amino acridines containing substituents such as halogen, nitro, alkyl, amino, alkoxy, or alkyl mercapto groups may be converted into alkyl sulfonic salts which are readily soluble in water Details are given of the production of the neutral dimethanesulfonate of 2-methoxy-6-chloro-9-(alpha-diethylamino-delta-pentylamino) acridine (melting point 125°C), the neutral diethane sulfonate and the neutral dibutanesulfonate of the same substituted acridine (melting points 200° and 158°C , respectively), all forming yellow crystals, and general mention is made of the production of other similar derivatives, which may be used in the treatment of malaria.

U S P 2,092,131
September 7, 1937

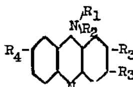
Mietzsch and Mauss
Assigned to Winthrop Chemical Co , Inc
Corresponds to D R P 632,733, E P 473,555, S P 183,560-
(Addition to 188,546, 189,062, 189,565)

9-amino- and 9-alkylamino-acridines are transformed into products which are readily and rapidly soluble in water by the manufacture of their salts with alkyl sulfonic acids The manufacture of these salts may be performed by neutralizing one molecule of the 9-amino acridine compound with one molecule of the alkyl sulfonic acid The alkyl sulfonates of the 9-amino acridine compounds may also be obtained by the known method of double decomposition of 9-amino acridine salts with salts of the alkyl sulfonic acids As alkyl sulfonic acid preferably the methane sulfonic acid is used, but also other salts with the 9-amino- and 9-alkylamino acridine compounds. These compounds are suitable for therapeutic use Many examples are given

U S P 2,113,357
April 5, 1938

Mietzsch and Mauss
Assigned to Winthrop Chemical Co , Inc
Corresponds to D R P 553,072, E P. 363,392, S P 154,953

Discloses 9-amino acridines of the general formula



wherein R_1 stands for an organic basic radical containing nitrogen, R_2 stands for hydrogen, an alkyl group or an organic basic radical containing nitrogen, R_3 stands for a halogen atom or an alkyl group and R_4 stands for hydrogen, a halogen atom, or an alkyl- or alkoxy group.

following compounds

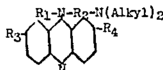
Position - 3	8	5
CH_3O-	Cl	$NH(CH_2)_2N(C_2H_5)_2$
CH_3O-	Cl	$NH(CH_2)_5N(C_2H_5)_2$
CH_3O-	Cl	$NH-CH(CH_3)(CH_2)_3N(C_2H_5)_2$
CH_3O-	Cl	$NH-CH[CH_2N(C_2H_5)_2]_2$
CH_3O-	Cl	$NHCH_2CHOHCH_2N(C_2H_5)_2$
CH_3O-	Cl	NH⟨ring⟩$N(C_2H_5)CH_2CH_2N(C_2H_5)_2$
CH_3O-	Cl	NH⟨ring⟩$OCH_2CH_2N(C_2H_5)_2$
CH_3O-	Cl	$NHCH_2CH_2N\langle CH_2-CH_2, CH_2-CH_2\rangle CH_2$
CH_3O-	Cl	$NH(CH_2)_2N(C_2H_5)CH_2CH_2N(C_2H_5)_2$
CH_3O-	Cl	$NHCH_2CH_2N(C_2H_5)_2$

Note that example 3 discloses Atebrine and Claim 7 covers the compound specifically

U S P 2,121,207
June 21, 1938

Mietzsch and Mauss
Assigned to Winthrop Chemical Co , Inc
Corresponds to D R P 632,224, B P 441,132

This patent relates to acridine compounds having the general formula



in which R_1 stands for hydrogen or alkyl, such as methyl or ethyl, R_2 stands for an aliphatic radical, such as methylene, ethylene, propylene, hydroxy propylene group or for alkylene groups which are interrupted by ether-like bound oxygen or sulfur atoms and R_3 and R_4 stand for alkyl, alkoxy, or alkyl thio groups, such as the methyl, ethyl, butyl, methoxy isopropyloxy, hydroxy propyloxy, methyl thio ethyl thio group and the like

Specifically disclosed are compounds such as the following

2,7-dimethoxy-9(α-diethylamino-delta-pentyl amino) acridine
2,7-dimethoxy-9(α-dimethylamino-β-ethyl amino) acridine
2,7-dimethoxy-9(α-diallylamino-γ-propyl amino) acridine
2,7-dimethoxy-9(α-diethylamino-δ-butyl amino) acridine
2,7-dimethoxy-9(α-diethylamino ethyl thio-γ-propyl amino) acridine
2,7-dimethoxy-9(α-diethylamino-β-hydroxy-γ-propylamino) acridine

injection are prepared by causing basically substituted amino acridines to react with alkyl sulfonic acids, or by double decomposition as by reaction of the sulfate of dialkyl aminoalkyl amino acridine with the barium salt of an alkyl sulfonic acid Basically substituted amino acridines containing substituents such as halogen, nitro, alkyl, amino, alkoxy, or alkyl mercapto groups may be converted into alkyl sulfonic salts which are readily soluble in water Details are given of the production of the neutral dimethanesulfonate of 2-methoxy-6-chloro-9-(alpha-diethylamino-delta-pentylamino) acridine (melting point 125°C), the neutral diethane sulfonate and the neutral dibutanesulfonate of the same substituted acridine (melting points 200° and 158°C , respectively), all forming yellow crystals, and general mention is made of the production of other similar derivatives, which may be used in the treatment of malaria.

U S P 2,092,131
September 7, 1937

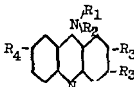
Mietzsch and Mauss
Assigned to Winthrop Chemical Co , Inc.
Corresponds to D R P 632,733, E P 473,555, S P 183,560-(Addition to 188,546, 189,062, 189,565)

9-amino- and 9-alkylamino-acridines are transformed into products which are readily and rapidly soluble in water by the manufacture of their salts with alkyl sulfonic acids The manufacture of these salts may be performed by neutralizing one molecule of the 9-amino acridine compound with one molecule of the alkyl sulfonic acid The alkyl sulfonates of the 9-amino acridine compounds may also be obtained by the known method of double decomposition of 9-amino acridine salts with salts of the alkyl sulfonic acids As alkyl sulfonic acid preferably the methane sulfonic acid is used, but also other salts with the 9-amino- and 9-alkylamino acridine compounds. These compounds are suitable for therapeutic use Many examples are given.

U.S.P. 2,113,357
April 5, 1938

Mietzsch and Mauss
Assigned to Winthrop Chemical Co , Inc
Corresponds to D R P 553,072, E P 363,392, S P 154,953

Discloses 9-amino acridines of the general formula



wherein R_1 stands for an organic basic radical containing nitrogen, R_2 stands for hydrogen, an alkyl group or an organic basic radical containing nitrogen, R_3 stands for a halogen atom or an alkyl group and R_4 stands for hydrogen, a halogen atom, or an alkyl- or alkoxy group

As examples this patent shows, among others, the following compounds

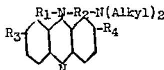
Position -	3	8	5
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	CH_3O-	Cl	$NH(CH_2)_5N(C_2H_5)_2$
	CH_3O-	Cl	$NH-CH(CH_3)(CH_2)_3N(C_2H_5)_2$
	CH_3O-	Cl	$NH-CH[CH_2N(C_2H_5)_2]_2$
	CH_3O-	Cl	$NHCH_2CHOHCH_2N(C_2H_5)_2$
	CH_3O-	Cl	$NH\langle\ \rangle N\langle^{C_2H_5}_{CH_2CH_2N(C_2H_5)_2}$
	CH_3O-	Cl	$NH\langle\ \rangle OCH_2CH_2N(C_2H_5)_2$
	CH_3O-	Cl	$NHCH_2CH_2N\langle^{CH_2-CH_2}_{CH_2-CH_2}\rangle CH_2$
	CH_3O-	Cl	$NH(CH_2)_2N\langle^{C_2H_5}_{CH_2CH_2N(C_2H_5)_2}$
	CH_3O-	Cl	$NHCH_2CH_2N(C_2H_5)_2$

Note that example 3 discloses Atebrine and Claim 7 covers the compound specifically

U S P 2,121,207 — June 21, 1938

Mietzsch and Mauss
Assigned to Winthrop Chemical Co , Inc
Corresponds to D R P 632,224, B P 441,132

This patent relates to acridine compounds having the general formula



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Specifically disclosed are compounds such as the following

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injection are prepared by causing basically substituted amino acridines to react with alkyl sulfonic acids, or by double decomposition as by reaction of the sulfate of dialkyl aminoalkyl amino acridine with the barium salt of an alkyl sulfonic acid Basically substituted amino acridines containing substituents such as halogen, nitro, alkyl, amino, alkoxy, or alkyl mercapto groups may be converted into alkyl sulfonic salts which are readily soluble in water Details are given of the production of the neutral dimethanesulfonate of 2-methoxy-6-chloro-9-(alpha-diethylamino-delta-pentylamino) acridine (melting point 125°C), the neutral diethane sulfonate and the neutral dibutanesulfonate of the same substituted acridine (melting points 200° and 158°C , respectively), all forming yellow crystals, and general mention is made of the production of other similar derivatives, which may be used in the treatment of malaria.

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September 7, 1937

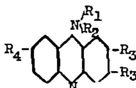
Mietzsch and Mauss
Assigned to Winthrop Chemical Co , Inc.
Corresponds to D R P 632,733, E P 473,555, S P 183,560-
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Assigned to Winthrop Chemical Co , Inc.
Corresponds to D R P 553,072, E P. 363,392, S P 154,953

Discloses 9-amino acridines of the general formula



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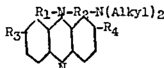
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	CH_3O-	Cl	$NH-CH(CH_3)(CH_2)_3N(C_2H_5)_2$
	CH_3O-	Cl	$NH-CH[CH_2N(C_2H_5)_2]_2$
	CH_3O-	Cl	$NHCH_2CHOHCH_2N(C_2H_5)_2$
	CH_3O-	Cl	NH⟨cyclohexylene⟩N(C_2H_5)($CH_2CH_2N(C_2H_5)_2$)
	CH_3O-	Cl	NH⟨cyclohexylene⟩$OCH_2CH_2N(C_2H_5)_2$
	CH_3O-	Cl	$NHCH_2CH_2N$ (CH_2--CH_2 / CH_2--CH_2) CH_2
	CH_3O-	Cl	$NH(CH_2)_2N(C_2H_5)(CH_2CH_2N(C_2H_5)_2)$
	CH_3O-	Cl	$NHCH_2CH_2N(C_2H_5)_2$

Note that example 3 discloses Atebrine and Claim 7 covers the compound specifically

U S P 2,121,207
June 21, 1938

Mietzsch and Mauss
Assigned to Winthrop Chemical Co , Inc
Corresponds to D R P 632,224, B P 441,132

This patent relates to acridine compounds having the general formula



in which R_1 stands for hydrogen or alkyl, such as methyl or ethyl, R_2 stands for an aliphatic radical, such as methylene, ethylene, propylene, hydroxy propylene group or for alkylene groups which are interrupted by ether-like bound oxygen or sulfur atoms and R_3 and R_4 stand for alkyl, alkoxy, or alkyl thio groups, such as the methyl, ethyl, butyl, methoxy isopropyloxy, hydroxy propyloxy, methyl thio, ethyl thio group and the like

Specifically disclosed are compounds such as the following

2,7-dimethoxy-9(α-diethylamino-delta-pentyl amino) acridine
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2,7-dimethoxy-9(α-diallylamino-γ-propyl amino) acridine
2,7-dimethoxy-9(α-diethylamino-δ-butyl amino) acridine
2,7-dimethoxy-9(α-diethylamino ethyl thio-γ-propyl amino) acridine
2,7-dimethoxy-9(α-diethylamino-β-hydroxy-γ-propylamino) acridine

2-isopropyloxy-7-methoxy-9(α-diethylamino-δ-pentyl amino) acridine.

Many other formulae of like nature are shown

German Patents

D R P 488,680
December 12, 1929

Eisleb and James
Corresponds to B P 283,510 January 11, 1928
S P 134,219, 137,134, January 10, 1928

Relates to the preparation of nitro-9-amino acridines which contain a further basic residue either in the 9-amino group or in the nucleus, by condensing a nitro-9-chlor acridine with a base containing at least 2 nitrogen atoms of which one is primary

Discloses formation of 2-ethoxy-6-nitro-9(β-diethyl-amino ethyl amino) acridine by heating 2-ethoxy-6-nitro-9-chlor acridine with phenol and condensing the resulting 9-phenyl ether, without isolation, with diethyl ethylene diamine

D R P 488,890
December 19, 1929

I G Farbenindustrie
Corresponds to U S P 1,706,403
Addition to D R P 486,079

D R P 490,418
January 9, 1930

Mietzsch
Assigned to I G Farbenindustrie

Relates to compounds of the type illustrated by the formula



D R P 498,661
May 8, 1930

Eisleb and James
Corresponds to B P 304,280 January 4, 1929
S P 138,146, January 13, 1928

D R P 553,072
June 2, 1932

Mietzsch and Mauss
Assigned to I G Farbenindustrie
Corresponds to U S P 2,113,357
B P 363,392

D R P 565,411
November 17, 1932

Mauss
Assigned to I G Farbenindustrie
Corresponds to U S P 1,855,302

D R P 571,449
February 28, 1933

Mauss and Mietzsch
Assigned to I G Farbenindustrie
Addition to D R P 553,072
Corresponds to S P 158,141, 154,953, 159,078

Relates to method for preparing acridine compounds having basic substituents in the 9 position, by reacting chlor acridine with amino alkylene amines

Discloses compounds such as

6-chlor-9(α-diethylamino-δ-pentyl amino) acridine
6-chlor-9(α-diethylamino-γ-butyl amino) acridine

D R P. 630,842
June 6, 1936

Mauss and Mietzsch
Assigned to I G Farbenindustrie
Addition to D R P 553,072 and D R P 571,449
Corresponds to B P. 437,953, May 4, 1934
S P 181,964, February 27, 1935
185,357, February 27, 1935

Discloses a method of preparing acridine compounds having alkyl mercapto groups in the 2 position and alkyl or halogen in the 6 and 9 positions

As examples cites compounds of the following type

2-methyl mercapto-6-chlor-9(α-diethylamino-δ-pentyl amino) acridine
2-ethyl mercapto-6-chlor-9(α-diethylamino-γ-propyl amino) acridine

D R P 631,504
June 24, 1936

Mietzsch and Mauss
Assigned to I G Farbenindustrie
Corresponds to U S P 2,077,249
B P 441,007
363,392

D R P 632,224

Mietzsch and Mauss
Assigned to I G Farbenindustrie
Corresponds to U S P 2,121,207
B P 441,132

D R P 632,733
July 13, 1936

Mietzsch and Mauss
Assigned to I G Farbenindustrie
Corresponds to U S P 2,092,131
B P. 473,555

D R P 642,758
March 24, 1937

Mietzsch, Mauss and Klarer
Assigned to I G Farbenindustrie
Corresponds to B P 466,505, November 28, 1935

Relates to the preparation of a series of acridine sulfonamides for use against blood parasites

Gives the following as examples

2-Methoxy-7-sulfondimethylamido-9(α-diethylamino,β-oxy-propylamino) acridine
2-Sulfondimethylamido-6-methyl-9(α-diethylamino,β-oxy-propylamino) acridine
2-Methoxy-7-sulfondiethylamido-9(α-diethylamino,β-ethyl-amino) acridine
2-Sulfondimethylamido-7-methyl-9(p-diethylamino ethoxy phenyl amino) acridine
2-Sulfondimethylamido-7-methyl-9(p-amino methyl phenyl amino) acridine

British Patents

For disclosures of the following list of British Patents see the corresponding American or German Patents

Brit P	U S P.	D R P
283,510		488,680
304,780		498,661
363,392	2,077,249	631,504
	2,113,357	553,072
367,037		555,934
437,953		630,842
441,007	2,077,249	631 504
441 132	2,121,207	632,224
454,375	2,092,131	632,733
466,505		642,758

British patents for which no corresponding U S P or German patent has been found.

B P 283,184
January 6, 1928

Chem Fabr vorm Sandoz

Powerful anti-parasitic compounds obtained by combination of amino and diamino acridines their alkyl halides and alkoxy derivatives with bile acids (desoxy cholic excluded)

B P 452,805
August 31, 1936

Soc des Usines Chemiques Rhone Poulenc

A salt of a 9-dialkylamino alkylene amino acridine is prepared by causing the acridine to react with an alkyl sulfonic acid or by double decomposition between a salt of the acridine and a soluble salt of an alkyl sulfonic acid whereby the inorganic salt radicals are precipitated These acridine sulfonic acid salts are crystalline, and very soluble in water furnishing neutral solutions suitable for injection In the examples 2-methoxy-6-chloro-9(α-diethylamino-δ-pentyl amino) acridine in alcohol is treated with methane or ethane sulfonic acids and the respective salts crystallized out on addition of EtOAc

Russian Patents

Russ Pat 38,629
35,832
38,628
35,837
42,998
(1938)

Knunyantz et al

Relate to preparation of dialkylamino alkylene amines.

Russ Pat. 48,307 (1936)

Magidson and Travin

Discloses condensation of 2-methoxy-6-cyan-9-chloro acridine with dialkylamino alkylene amines in the presence of phenols at elevated temperatures. The product comprises 2-methoxy-6-cyan-9(δ-n-diethyl amino-α-methyl butyl amino) acridine when diethyl amino-4-amino pentane is used

Russ Pat 50,629 (1937)

Strukov

Preparation of nitro acridine by heating nitro anisidine and glycerol in the presence of arsenic and sulfuric acids to 100-120° C in vacuo until water is no longer distilled off.

Russ Pat 50,660 (1937)

Grigorowsky

Discloses the purification of 2-methoxy-6-chloro-9-δ-diethyl amino methyl butyl amino acridine by treating with aqueous acetone, filtering and drying.

Russ Pat 51,908 (1937)

Drosdov

9-chloro acridine heated with dialkyl aniline in the presence of $AlCl_3$ to produce 9(dialkyl amino phenyl) acridines

Russ Pat. 53,030 (1938)

Magidson and Grigorowsky

Discloses the treatment of 2-methoxy-6-chloro-9-(diethyl amino isopentyl) acridine with lactic acid in an organic solvent i e alcohol, acetone, ether, etc) and the purification of the lactate by crystallization.

Russ Pat 53,169 (1938)

Gerchuk

Conversion of 9-chloro acridine or its derivatives to the corresponding amino compound by passing a stream of ammonia through a solution thereof at atmospheric pressure.

Fr P 832,542 September 28, 1938	Altman Corresponds to Dutch patent 42,540

Decomposition products of castor oil converted to $R_2NCH_2(CH\ )_{8-9}CH_2Cl$ and reacted with acridines Discloses 3-chloro-8-methoxy-10-diethylamino-11'-undecyl amino acridine and 3-chloro-8-methoxy-10-diethyl amino-12'-dodecyl amino acridine

Can P 367,733 August 3, 1937	Mietzsch and Lauss Assigned to Winthrop Chemical Co Inc

Therapeutic antiparasitic acridine compounds are prepared by reaction of a base or its salt containing at least 2 basic N atoms one present in the form of a primary or secondary amino group, with acridine containing in the 9-position a replaceable substituent such as halogen, in the 6-position a halogen atom or an alkyl group and in the 2 position an alkyl mercapto group or an alkoxy group of at least 3 carbon atoms

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(20) Chopra, R N - Calcutta Med. J 34, 183-93(1938)

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(22) Chopra, R N and Das Gupta, B M - Ind med gaz 68, 493(1933)

(23) Chopra, R N , Das Gupta, B M. and Roy, A C. - Ind med gaz 71, 710(1936)

(24) Chopra, R N Ganguli, S K - Ind med gaz 70, 313-20(1935)

(25) Chopra, R N , Ganguli, S K and Roy, A C - Ind med gaz 71, 443(1936)

(26) Chopra, R N , Gupta, J C and Genguli, S K - Ind med gaz 68, 558-60 (1933)

(27) Chopra, R N , Hayter, R T M , Sen B and M Talukdar - Ind med gaz 75, 202-04(1940) Drug & Cos Ind 47, No 6, 709(1940)

(28) Chopra, R N and Mukherjee, S N - Ind med gaz 71, 34(1936)

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(31) Chopra, R N and Abdul-Wahed, A K M - Ind med gaz 69, 213-14(1934)

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